Conclusions: The aromatase inhibitor, letrozole was found to be associated with higher pregnancy rate as compared to exogenous steroid supplementation in frozen-thawed embryo transfer cycles. Findings suggest that higher estradiol levels during exogenous steroid supplementation may affect the implantation window.

INVITED SESSION

Session 28: Live surgery

08 July 2008 **10:00–13:00**

SELECTED ORAL COMMUNICATION SESSION

Session 29: Early pregnancy - Clinical aspects

08 July 2008 **10:00–11:30**

O-104 Oral Can serial measurements of inhibin A and activin A be used to predict the outcome of pregnancies of unknown location?

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Introduction: A 'pregnancy of unknown location' (PUL) is defined by the finding of an empty uterus with no signs of an intra-uterine or extra-uterine pregnancy on a transvaginal ultrasound scan in a woman with a positive pregnancy test. There are three possible final clinical outcomes – failing PUL, intrauterine pregnancy (IUP) and ectopic pregnancy (EP). At present serial measurements of serum human chorionic gonadotrophin (hCG) are often used to help predict the final clinical outcome. Inhibin A and activin A are glycoproteins secreted by the feto-placental unit. Previous studies have suggested that inhibin A is a specific marker of early pregnancy loss, with lower levels found in spontaneous miscarriages. Activin A is thought to be a marker of trophoblastic invasion with the potential to identify patients at risk of ectopic pregnancy (EP). The aim of this study was therefore to evaluate the role of serial measurements of inhibin A and activin A in the prediction of the outcome of pregnancies of unknown location (PULs).
Materials and methods: This was a prospective observational study on women classified as having a PUL attending an Early Pregnancy Unit. All women were followed up until the final pregnancy outcome was known – failing PUL, IUP or EP. Serum hCG, inhibin A and activin A levels were measured at presentation (0 hours) and 48 hours later. The mean hCG, inhibin and activin levels and the change in levels over 48 hours expressed as a ratio (48 hours/0 hours) were incorporated into multi-category logistic regression models to predict all pregnancy outcomes. The performance of the models was evaluated using receiver operator characteristic (ROC) curves.
Results: 141 women classified with PULs were included in the study. The final clinical outcomes were: 67 failing PULs (47.5%), 58 IUPs (41.1%) and 16 EPs (11.4%). The logistic regression model based on serum inhibin levels gave an area under the curve (AUC) of 0.896 for failing PUL, 0.878 for IUP and 0.648 for EP. The model based on serum activin levels gave an AUC of 0.591 for failing PUL, 0.596 for IUP and 0.544 for EP and finally the model based on serum hCG levels gave an AUC of 0.955 for failing PUL, 0.970 for IUP and 0.690 for EP.
Conclusions: Serum activin A levels at 0 and 48 hours are not helpful in predicting the outcome of PULs. Although serum inhibin A levels may be of use in the prediction of failing PULs and IUPs in the PUL populations, they do not perform as well as serum hCG levels.

O-105 Oral Guideline adherence in the management of ectopic pregnancy

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Introduction: Evidence based guidelines are regarded important instruments to improve quality of care and efficiency and they reduce practice variation. The implementation of guidelines, however, is often problematic. To assess whether guidelines are truly implemented, it is of importance to measure quality of care. To measure quality of care, we developed a set of indicators for the management of women with ectopic pregnancy (EP) and assessed the adherence to the Dutch guideline on the management of EP using these indicators. This guideline provides a diagnostic algorithm - using transvaginal sonography (TVS) combined with serum human chorionic gonadotrophin (hCG) measurement - for women with suspected EP and evidence based treatment options.
Materials and methods: The systematic RAND-modified Delphi-method was used to develop quality indicators based on the Dutch guideline on the management of EP1. This stepwise method consists of three expert consensus rounds to appraise recommendations in terms of health gain, efficacy, measurability and capacity for improvement of care. These representative quality indicators were used to evaluate the process of care of women with EP in the period 2003–2005 in two academic, two teaching and two non teaching hospitals in The Netherlands.

Women were identified from hospital registries, after which their medical charts were scored. For each quality indicator, a ratio was calculated for adherence to the guideline. For example, guideline adherence for the indicator "laparoscopic surgery" was expressed as the number of laparoscopically treated women (numerator) divided by the overall number of surgically treated women (denominator).
Results: Out of 30 recommendations, 12 quality indicators were selected and used to asses the management of 325 women with EP. Aspects of the diagnostic algorithm were regarded as procedural indicators ($n = 7$). Structural indicators ($n = 2$) implicated laboratory and theatre availability. Outcome indicators ($n = 3$) concerned surgical treatment.

Transvaginal sonography (TVS) was well incorporated in the diagnostic workup as demonstrated by its use in 99% of women. In case of an inconclusive TVS, serum hCG was only measured in 86% of women. Round the clock laboratory service for serum hCG measurement was available in four of the six hospitals. If EP was diagnosed according to the algorithm, 75% of women were admitted the same or the following day for surgery. If the diagnosis at first visit was not EP according to the algorithm, 40% of women were surgically treated, instead of a follow up visit after 48 hours consistent with the algorithm.

Laparoscopy was the first choice of surgery in 94% of women and succeeded in 90% of these, while a conversion to laparotomy was necessary in 10%. During out of office hours (18.00–08.00 hours), laparoscopy remained the preferred surgical approach and the percentage of conversions to laparotomy did not differ from day time surgery. At night time (23.00–08.00 hours), salpingostomy was less frequently attempted than during daytime (40% versus 27%), however less conversions to salpingectomy were needed (4% versus 17%).

In women with contra lateral tubal pathology, a salpingostomy was only attempted in 31%. This tube conservative approach was not successful in 36% resulting in conversion to salpingectomy.

To detect persistent trophoblast (PT) after salpingostomy, serum hCG follow-up was only completed in 81% of women. The PT rate was 10% and this complication was preferably treated with systemic methotrexate (88%). Blood was not typed in 5%, while only 46% of Rhesus negative women received anti D immuno prophylaxis.
Conclusions: The 12 quality indicators accurately monitored EP care. The overall adherence to the guideline was reasonable, but several aspects of the diagnostic process and treatment need improvement. Further research should focus on the barriers and facilitators to better understand and improve guideline adherence and EP care.

Reference

S.M. Mourad, *et al.* Guideline-based development of quality indicators for sub fertility care. *Hum Reprod* 2007;**22**:2665–2672.

O-106 Oral A new statistical method for longitudinal assessment of early fetal growth - prospective testing of a functional linear discriminant analysis model

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Introduction: Most assessments of early fetal growth use cross-sectional data comparing the growth of individual fetuses at one time point. Reduced growth even in the early first trimester is associated with an increased risk of first trimester miscarriage. Functional linear discriminant analysis (FLDA) is an extension of classical linear discriminant analysis to longitudinal data, distinguishing between outcome groups by maximizing ratio of between-class variation to within-class variation, used to assess rate of growth for individual fetuses. A preliminary study has shown that it is possible to discriminate between fetuses destined to miscarry and those which will remain viable using longitudinal growth measurements. The aim of this present study is to apply this model to a further population from the same institution and from an alternative institution to determine whether it can prospectively predict miscarriage.

Materials and methods: Observational study of women attending an early pregnancy unit at a teaching hospital in London, UK and a university hospital in Leuven, Belgium. Inclusion criteria were singleton pregnancy, certain and regular menstrual dates and known outcome at 11–14 weeks, with at least two TVS assessments showing a viable fetus in the first trimester. Women were classed into those with viable pregnancies at 11–14 weeks (class 1) and those with miscarriage by 11–14 weeks (class 2).

The FLDA model developed on a training dataset was applied to the data from women in London (same institution as training data) and Leuven (different institution).

Results: The results of the application and testing of the model for the two groups will be presented, with sensitivities and specificities for the test to predict early pregnancy loss.

Conclusions: Preliminary FLDA results suggest that impaired rate of growth in the early first trimester can predict miscarriage with high sensitivity and specificity. This prospective testing study will show whether FLDA has the power to reliably predict early pregnancy loss using the rate of change of MSD or MSD-CRL in patients where MSD and CRL have been measured on at least two occasions.

If confirmed, on the results to be presented, this would provide a powerful tool for identifying women very likely to undergo miscarriage by the end of the first trimester.

O-107 Oral Effect of Body Mass Index on pregnancy outcome in women with recurrent miscarriage

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Introduction: A recognised cause for recurrent miscarriage (RM) ($\geq$3 miscarriages) is identified in less than 50% of couples. These couples, labelled as having 'unexplained' RM, are said to have a good chance of a future successful pregnancy with supportive care alone. A raised Body Mass Index (BMI) is recognised to be associated with infertility, sporadic miscarriage and later pregnancy complications.

The aim of this study was to determine the relationship between maternal BMI and future pregnancy outcome amongst couples who, after comprehensive investigation, are designated as having 'unexplained' RM.

Materials and methods: All couples referred to our clinic have peripheral blood karyotyping performed. In addition, the female partner has a pelvic ultrasound scan to determine uterine anatomy, screening for antiphospholipid antibodies (lupus anticoagulant and both IgG and IgM anticardiolipin antibodies) and activated protein C resistance together with genotyping for the Factor V Leiden mutation. Couples with normal investigations are designated as having 'unexplained' RM.

The outcome of the next pregnancy amongst 398 women with a history of RM (median age 35 years; range 17–47) and a diagnosis of unexplained RM who attended the clinic between 1996–2006 was studied. Women were divided into 4 groups (WHO criteria) based on BMI - underweight (BMI $<$ 18.5 kg/m^2), normal (BMI 19–24.9 kg/m^2), overweight (BMI 25–29.9 kg/m^2) and obese (BMI $\geq$30 kg/m^2). Maternal BMI and pregnancy outcomes were compared and analysed by logistic regression analysis.

Results: BMI distribution in the study group showed 1% (5/398) to be underweight, 49% (193/398) to be of normal weight, 34% (137/398) to be overweight and 16% (63/398) obese. Of these women 79% were Caucasian, 11% Afro-Caribbean, 9% Asian and 1% Oriental. Amongst the women who miscarried in their next pregnancy, 0.5% (1/207) were underweight, 44.9% (93/207) had normal BMI, 33.3% (69/207) were overweight and 21.3% (44/207) were obese.

Obese women had a significantly increased risk of miscarriage compared to those of normal weight [OR 2.30 (CI = 1.18–4.47)]. There was no difference in the miscarriage rate amongst those who were either overweight [OR 1.39 (CI = 0.88–2.20)] or underweight [OR 0.28 (CI = 0.03–2.54)] compared with those of normal weight.

Logistic regression analysis in the unexplained RM group showed increased maternal age ($<$35 and $\geq$35) and number of previous miscarriages ($\leq$4 and $\geq$5) were significantly associated with poor outcome with [OR 1.60 (CI = 1.05–2.43)] and [OR 1.87 (CI = 1.10–3.18)] respectively.

Conclusions: This study demonstrated that women with unexplained RM who have a BMI $\geq$ 30 kg/m^2 have a significantly increased risk of miscarriage in future untreated pregnancies compared to those with a normal BMI. These data should be used in counselling women regarding the significant beneficial effect on pregnancy outcome to be gained by weight loss.

O-108 Oral Vanishing fetuses following assisted reproduction is an independent negative factor for a healthy outcome

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Objective: Vanishing fetal syndrome, the identification of a multifetal gestation with subsequent disappearance of one or more fetuses, occurs infrequently in nature due to the limited occurance of multiple pregnancies. In contrast with the epidemic of multiple gestations in women undergoing assisted reproduction, both multiple pregnancies and vanishing fetuses have become more obvious in clinical practice. However, there is little information in the medical literature about the impact of a vanishing twin in early pregnancy on pregnancy outcome. The aim of the present study is to compare a cohort analysis of women pregnant with multiple gestations and experienced a vanishing twin in comparison with a randomly selected group of women with similar demographics and cycle characteristics, but with only a singleton pregnancy.

Participants and methods: One-hundred and ninety five women with multiple pregnancies (156 twin pregnancies and 39 high-order pregnancies) and vanishing fetal syndrome following assisted reproduction were included in the cohort. They were compared with a group of one thousand women with a singleton pregnancy following assisted reproduction, with all having follow-up till delivery. The primary outcome measures were gestational age and percentage of term deliveries in the two groups. The secondary outcomes were the incidence of stillbirths, live-birth, neonatal deaths, and average fetal weight following delivery. Subgroup analysis was conducted for the vanishing fetal group according to original number of sacs (i.e. twin vanishing group and high-order multiple pregnancy vanishing group).

Statistical analysis was performed using the computer statistical package Stats Direct (Stats Direct Ltd, UK). All analyses of significance were two-sided and tested at the 5% level; values of $P < 0.05$ were considered to indicate significant differences. Continuous variables were tested if they presented normal distribution using the f-test. The results of the two groups were compared using the t-test or Mann-Whitney U test for parametric and nonparametric data, respectively. Qualitative variables were compared using the chi-squared test with Yates correction or Fisher's exact test, when necessary.

Results: There were no significant differences in patient age [30.18 (4.51) versus 29.92 (4.73), number of oocytes retrieved [13.10 (5.87) versus 13.12

(6.08)], or number of transferred embryos [3.09 (0.52) versus 3.09 (0.56)] between the two groups. Also there were no significant differences in the incidence of live births [0.97 (0.18) versus 0.96 (0.20)] and stillbirths [0.03 (0.18) versus 0.04 (0.20)]. However, the women in the singleton pregnancy group had a significantly longer mean gestation of pregnancy [37.05 (2.98) versus 36.24 (3.58); $P = 0.001$] and a lesser likelihood of having a preterm delivery (93% versus 85%; $P = 0.006$) than the vanishing fetal group. In addition, the singleton group had a greater mean birth weight (2978 (490) versus 2832 (579); $P = .0241$) than the vanishing fetal group. On subgroup analysis of multiple pregnancy, the vanishing high-order group had the highest incidence of a neonatal death compared with the vanishing twin group ($P = 0.03$) or singleton group ($P = 0.04$). The other comparisons were not significantly different.
Conclusions: Vanishing fetuses are under-emphasized as a negative variable on the outcome of pregnancy in women with multiple gestations. Future studies should focus on determining the underlying causes of vanishing fetuses and the exact mechanism of effect on pregnancy outcomes.

O-109 Oral Revisiting very early first trimester growth–influence of ethnic background and maternal age using transvaginal ultrasonography (TVS)

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Introduction: There is increasing evidence that growth restriction may be evident in the first trimester and this may predict first trimester miscarriage or adverse outcome in the second and third trimesters. Growth studies in later pregnancy suggest an ethnic variation in growth of the fetus but early pregnancy growth studies have used only homogenous populations of normal singleton pregnancies. Previous studies have not looked at the influence of maternal age or ethnic background on early first trimester growth. The objective was to determine whether ethnic background or maternal age affect growth in the first trimester using modern high frequency transvaginal sonography.
Materials and methods: Prospective observational study of 1828 women attending for TVS prior to 12 weeks gestation. Women were included in the analysis if they had singleton pregnancies, certain dates, regular cycles, spontaneous conception and known normal outcome at 11–14 weeks gestation with no reported fetal abnormality. Ethnic origin, maternal age, gestational age, certainty of menstrual dates and presence of vaginal bleeding were recorded prior to structured TVS assessment and measurement of gestational sac, yolk sac and crown rump length. Crown rump length (CRL) and other variables containing growth data such as mean gestation sac diameter (MSD), mean yolk sac diameter (MYD), CRL/MSD, MSD-CRL and MSD–MYD were assessed as a function of gestational age. Stepwise multilinear regression analysis was performed to determine which variables (maternal age, ethnic background or vaginal bleeding) affected the rate of change of the variable according to gestational age (measurements included up to 98 days gestation).
Results: 455 women met the inclusion criteria, providing 1082 cross sectional data points. The number of scans per patient ranged from 1 to 8. Mean maternal age was 31.3 years (range 17–44). 17% were black, 66% white, 14% Asian and 3% mixed origin. Gestational age at time of measurements ranged from 37 to 94 days. Maternal age significantly influenced the CRL - as maternal age increased a smaller CRL was observed at lower gestational ages ($P < 0.0001$) but there was a significantly larger rate of increase in CRL with gestational age ($P < 0.0001$). Maternal age also significantly influenced the rate of change of MSD, the difference between MSD and CRL, the ratio CRL/MSD and the ratio MYS/MSD with gestational age. Black ethnic origin was associated with a significantly increased rate of change in CRL ($P < 0.0001$). Ethnicity also influenced MSD, the ratio CRL/MSD, MYS and the ratio MYS/CRL. A nonlinear regression model of CRL for black and non-black ethnic background suggests that non-black growth is similar to that demonstrated by Robinson growth curves, while black background is associated with an increased growth rate in the first trimester. Growth charts for black and non-black populations which adjust for maternal age have been developed for use between 37–85 gestational days. None of the growth variables differed significantly between those with or without vaginal bleeding.
Conclusions: Rate of growth of CRL appears to be greater in black than non-black fetuses during the first trimester. CRL appears to be initially smaller as maternal age increases but rate of growth is greater than in younger women. Other growth variables incorporating MSD and MYS are also significantly influenced by ethnic background and maternal age. Separate CRL growth curves have been developed for black and nonblack populations and for different maternal ages. As CRL is used to date pregnancies which subsequently forms the basis of growth assessment in later pregnancy, accurate growth charts should be used based on this new evidence of ethnic and maternal age variation in the first trimester.

SELECTED ORAL COMMUNICATION SESSION

Session 30: ART - Clinical - Single embryo transfer

08 July 2008 **10:00–11:30**

O-110 Oral Single embryo transfer reduces clinical pregnancy rates in fresh IVF and ICSI cycles: an obstacle to rapid expansion

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Introduction: The increasing success of in-vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) is complicated by an increased risk of twin or higher multiple pregnancies. In Europe (EIM Consortium, 2003), 15.7% of IVF/ICSI cycles involved the transfer of one embryo only, the exceptions being the Nordic Countries and Belgium (≥40%), 8.2% in the USA (SART, 2004), and 10% in Latin America (REDLARA–2003/2004). Single embryo transfer significantly reduces the risk of multiple pregnancies but can also decrease the chance of clinical pregnancies in IVF/ICSI cycles. The aim of this meta-analysis was to compare current data on single embryo versus double embryo transfer in fresh IVF/ICSI cycles with respect to ongoing clinical pregnancy rate.
Materials and methods: Search strategies included on-line databases (MEDLINE, EMBASE, Science Citation Index, Cochrane Controlled Trials Register and OVID) from 1995 to 2007. There was no language restriction. The following headings and text strings were used: assisted reproductive technology, multiple pregnancy, randomized controlled trial, single embryo transfer, double embryo transfer. The primary outcome measure was ongoing clinical pregnancy rate. Only randomized studies were included in this meta-analysis. Following Medical Subject, the pooled odds ratio (OR) was equal to 1. The fixed effect was used. A confidence interval for the Mantel-Haenszel odds ratio was calculated using the Robins, Breslow, and Greenland fixed effect variance formulas. Heterogeneity (non-combinability) was evaluated by Cochran's Q, the Breslow-Day, and I^2 tests. Data were managed and analyzed using StatsDirect statistical software (Cheshire, UK).
Results: Six trials fulfilled the inclusion criteria. Using the fixed effect model (Figure 1), pooling results showed a higher statistically significant ongoing clinical pregnancy rate when double embryo transfer (45.1%; 298/660) was compared with single embryo transfer (28.4; 188/661) ($P < 0.0001$; OR: 2.09, 95% CI = 1.66 to 2.64). There was no heterogeneity in this comparison (Breslow-Day = 2.86, df = 5, $P = 0.72$; Cochran Q = 2.84, df = 5, $P = 0.72$; $I^2 = 0\%$).