system tumors [ever use (HR, 5.79; 95% CI, 1.23–27.24) and >3 cycles of use (HR, 8.51; 95% CI, 1.72–42.19)] markedly.

Limitations, reason for caution: Although we tried to minimize the effects of the underlying infertility, the severity of infertility can have affected our risk estimates as women with more severe fertility problems may receive more treatment. Furthermore, as we conducted multiple statistical tests some results may have been due to chance findings.

Wider implications of the findings: Additional large epidemiological studies are pressingly needed to confirm our finding. Although potential adverse effects of fertility treatment must be put into perspective and balanced against the benefits of childbirth, it may be considered if specialists should consider the increased risk when performing fertility treatment and if couples seeking fertility treatment should be informed.

Study funding/competing interest(s): Funding by national/international organization(s). This work was supported by a grant from BørneCancerFonden (Childhood Cancer Foundation). The funding organization had no role in the design and conduct of the study; the collection, management, analyses, and interpretation of the data; or the preparation or approval of the manuscript.

Trial registration number: Not applicable.

SELECTED ORAL COMMUNICATION SESSION
SESSION 44: UNDERLYING MECHANISMS OF EARLY PREGNANCY PATHOLOGY
Tuesday 1 July 2014 15:15 - 16:30

O-166 Inflammatory cytokines in the placenta and maternal circulation of chromosomally abnormal first trimester miscarriages
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Study question: The impact of abnormal placental karyotype on the inflammatory response within the villous tissue and peripheral circulation of women with miscarriage was evaluated.

Summary answer: In miscarriage with abnormal karyotype, there is an exacerbated placental inflammatory response, in contrast to miscarriage of normal karyotype where maternal systemic response is increased.

What is known already: Cytokines at the feto-maternal interface plays an important role in determining the outcome of a particular pregnancy.

Study design, size, duration: Consent was obtained prospectively from 106 women presenting with a missed miscarriage, undergoing ERPC at UCLH over a period of 10 months. Karyotyping of the miscarried chorionic villous samples resulted in 29 cases with normal male karyotype and 25 with abnormal male karyotype.

Participants/materials, setting, methods: Villous and venous blood samples were obtained from women with missed miscarriage. T Concentration of tumour necrosis factor alpha (TNFα), TNF-R1 and TNF-R2, and interleukin (IL)-10 were measured using flowcytometric bead array in fresh villous homogenate, cultured villous extracts, culture medium, maternal whole blood, and plasma.

Main results and the role of chance: Plasma TNFα/IL-10 ratios were significantly (p < 0.05) lower in miscarriages with abnormal karyotype. In the abnormal karyotype group, there were significantly higher levels of TNFα (p < 0.01), IL-10 (p < 0.01), TNF-R1 (p < 0.001), and TNF-R2 (p < 0.001) in the villous extracts and culture-conditioned medium compared to normal karyotype group.

Limitations, reason for caution: Only miscarried pregnancies with a male karyotype fetus were included, to avoid the risk of maternal contamination during interpretation of the results.

Wider implications of the findings: This study gives a better insight into the mechanisms involved during miscarriage, and may pave the way for predicting the risk of miscarriage and other placental-related adverse pregnancy outcomes, such as pre-eclampsia, intra-uterine growth restriction and preterm delivery.

Study funding/competing interest(s): Funding by hospital/clinic(s), UCLH charities for early pregnancy research.

Trial registration number: Not applicable.

O-167 Standardisation of uterine natural killer (uNK) cell measurements in endometrium of women with recurrent miscarriage
G.E. Lash1, S.M. Laird1, T.C. Li2, I.A. Innes3, N. Mariee4, N. Patel5, S.M. Quenby1, J.N. Bulmer1
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2Sheffield Hallam University, Biomedical Research Centre, Sheffield, United Kingdom
3University of Warwick, Biomedical Research Unit in Reproductive Health, Coventry, United Kingdom

Study question: Can assessment of density of uterine natural killer (uNK) cells be standardised across different research laboratories?

Summary answer: Analysis of the same fifteen sections in three different centres showed variation which could be attributed to tissue processing, image capture, where in the tissue sample assessment images were taken and what was counted as an immunopositive cell. A standardised protocol has been agreed and is currently being tested.

What is known already: Several studies have demonstrated that uNK cells are increased in mid-luteal phase endometrium in a subset of women with recurrent miscarriage (RM) and recurrent implantation failure (RIF). However, what is classified as “high” density varies between research groups. In addition, whether this increase in uNK cell numbers contributes to the aetiology of the condition or is a marker of widespread endometrial dysfunction is unclear.

Study design, size, duration: Three centres participated in the study. Each centre exchanged 5 × 3 µm formalin fixed paraffin embedded sections of endometrium from women with recurrent miscarriage or after hysterectomy for non-malignant conditions from 5 different cases.

Participants/materials, setting, methods: Sections were immunostained for CD56 in routine pathology or research laboratories. Images were taken of 10, 40x random fields of view that contained the luminal epithelium, total stromal and immunopositive uNK cells were counted manually in Image J and results expressed as % positive uNK cells/stromal cells.

Main results and the role of chance: Each sample was immunostained 5 times across 3 different centres with different methods (Newcastle - 2x research laboratory and 1x pathology laboratory; Sheffield - research laboratory; Warwick – pathology laboratory). The level of variation in % immunopositive uNK cells differed for each of the 15 different samples assessed in the 5 different settings (variance: mean ± SEM 17.4 ± 5.9; range: 0.16–71.3; coefficient of variation: mean ± SEM 0.4 ± 0.05; range: 0.18–0.88; range: mean ± SEM 7.7 ± 1.7, range: 1.0–19.5). The variation could be attributed to length of tissue fixation, potential accumulation of dust in water baths and processing stations, selection of areas for assessment, quality of image analysis, definition of immunopositive cells, and inclusion or exclusion of notable blood vessels.

Limitations, reason for caution: This study confirms the variation in uNK cell measurement in different centres even on the same cases. A standardised protocol has been agreed and is currently being tested to assess its ability to reduce the variation.

Wider implications of the findings: From time to time women with RM or RIF request uNK cell density testing. It is not clear whether the association between “high” uNK cell density and these conditions is causal, nor whether “high” uNK cell density predicts poor outcomes or need for treatment. However, standardisation of testing is urgently needed to foster collaboration and progress in this field.

Study funding/competing interest(s): Funding by University(ies), Newcastle University; Sheffield Hallam University; University of Warwick.

Trial registration number: Not applicable.

O-168 Relation between cytokine gene polymorphisms and concentration of autoantibodies and CD markers in Iranian recurrent miscarriage patients
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3Avicenna Research Institute ACECR, Reproductive Biotechnology Research Center, Tehran, Iran
4Avicenna Research Institute ACECR, Reproductive Immunology Research Center, Tehran, Iran

Study question: Can assessment of density of uterine natural killer (uNK) cells be standardised across different research laboratories?

Summary answer: Analysis of the same fifteen sections in three different centres showed variation which could be attributed to tissue processing, image capture, where in the tissue sample assessment images were taken and what was counted as an immunopositive cell. A standardised protocol has been agreed and is currently being tested.

What is known already: Several studies have demonstrated that uNK cells are increased in mid-luteal phase endometrium in a subset of women with recurrent miscarriage (RM) and recurrent implantation failure (RIF). However, what is classified as “high” density varies between research groups. In addition, whether this increase in uNK cell numbers contributes to the aetiology of the condition or is a marker of widespread endometrial dysfunction is unclear.

Study design, size, duration: Three centres participated in the study. Each centre exchanged 5 × 3 µm formalin fixed paraffin embedded sections of endometrium from women with recurrent miscarriage or after hysterectomy for non-malignant conditions from 5 different cases.

Participants/materials, setting, methods: Sections were immunostained for CD56 in routine pathology or research laboratories. Images were taken of 10, 40x random fields of view that contained the luminal epithelium, total stromal and immunopositive uNK cells were counted manually in Image J and results expressed as % positive uNK cells/stromal cells.

Main results and the role of chance: Each sample was immunostained 5 times across 3 different centres with different methods (Newcastle - 2x research laboratory and 1x pathology laboratory; Sheffield – research laboratory; Warwick – pathology laboratory). The level of variation in % immunopositive uNK cells differed for each of the 15 different samples assessed in the 5 different settings (variance: mean ± SEM 17.4 ± 5.9; range: 0.16–71.3; coefficient of variation: mean ± SEM 0.4 ± 0.05; range: 0.18–0.88; range: mean ± SEM 7.7 ± 1.7, range: 1.0–19.5). The variation could be attributed to length of tissue fixation, potential accumulation of dust in water baths and processing stations, selection of areas for assessment, quality of image analysis, definition of immunopositive cells, and inclusion or exclusion of notable blood vessels.

Limitations, reason for caution: This study confirms the variation in uNK cell measurement in different centres even on the same cases. A standardised protocol has been agreed and is currently being tested to assess its ability to reduce the variation.

Wider implications of the findings: From time to time women with RM or RIF request uNK cell density testing. It is not clear whether the association between “high” uNK cell density and these conditions is causal, nor whether “high” uNK cell density predicts poor outcomes or need for treatment. However, standardisation of testing is urgently needed to foster collaboration and progress in this field.

Study funding/competing interest(s): Funding by University(ies), Newcastle University; Sheffield Hallam University; University of Warwick.

Trial registration number: Not applicable.
Study question: Which cytokine gene polymorphisms (IL-6, IL-1β, IL-10, IL-13 and IL-17) are related to autoantibodies (anti-nuclear Rel, anti-dsDNA, anti-cardiolipin Ab, anti-thyroid peroxidase, anti-thyroglobulin) and CD markers (CD3, CD4, CD8, CD4/8, CD5, CD19, CD15, CD65, CD56, CD16/56) as risk of recurrent miscarriage (RM)?

Summary answer: It seems 2 polymorphisms of IL-10 (−819 and −592) are related with CD5, CD5/19, CD56 and CD16/56 that maybe increased the risk of RM.

What is known already: This is the first study that evaluated the relation of 10 polymorphisms of 6 cytokine genes with concentration of autoantibodies and CD markers in recurrent miscarriage.

Study design, size, duration: In this case–control study, 104 women with history of at least three miscarriages were recruited between April 2010 and March 2011 as the case group. Seventy healthy women with a history of two successful deliveries, without any pregnancy complications, were also selected as the control group.

Participants/materials, setting, methods: IL-1β (−31, −511 and +3954), IL-1RN (+9589 and +11100), IL-6 (−174), IL-10 (−819, −591 and −1082), IL-13 (+2044) and IL-17 (−197) polymorphisms were compared in patients and healthy controls using a PCR-RFLP. The data about autoantibody concentrations and CD markers were collected from patient records.

Main results and the role of chance: The data showed significant differences in IL-10 promoter gene polymorphism (−592 and −819) frequencies between RM patients and healthy controls (p < 0.01). However no significant differences in the frequencies of interleukin IL-1β, IL-1RN, IL-6, IL-10 (−1082), IL-13 and IL-17 polymorphisms were detected between RM patients and healthy controls. Significant differences in the frequencies of CDS (p < 0.001, p = 0.035), CD519 (p < 0.001), CD516 (p = 0.002, p = 0.016) and CD16/56 (p = 0.002, p = 0.001) positive cells were found between RM patients carrying different genotypes of IL-10 (−819, −591) (normal, heterozygous and homozygous) and IL-10 −592, respectively, but not other cytokine gene polymorphisms.

Limitations, reason for caution: Because the sample size was relatively small in the study, we could not confirm polymorphisms of IL-10 (−819 and −592) as a predictive marker for RM. Therefore a larger study is needed to warrant this information.

Wider implications of the findings: Although a large study population was included immunological testing was performed only once during the menstrual cycle and therefore cycle-specific differences can not be excluded.

Study funding/competing interest(s): No trial registration number.

Trial registration number: A trial registration number was not required due to the retrospective study design.

O-170 An early pregnancy assessment unit improves quality of care and reduces health care costs

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Study question: What is the impact of an early pregnancy assessment unit (EP AU) on clinical care in women with early pregnancy complications? What is known already: An EP AU helps streamlining the service for women with suspected miscarriage or ectopic pregnancy, and for women with history of recurrent miscarriage. Whether EP AUs improve the quality of care for women with early pregnancy complications and health care costs were halved for the diagnosis and treatment in women with miscarriage and a history of recurrent miscarriage.

Summary answer: In a University Hospital setting, the establishment of an EP AU improved the quality of care for women with early pregnancy complications and health care costs were halved for the diagnosis and treatment in women with miscarriage and a history of recurrent miscarriage.

What is known already: An EP AU helps streamlining the service for women with suspected miscarriage or ectopic pregnancy, and for women with history of recurrent miscarriage. Whether EP AUs improve the quality of care for women with early pregnancy complications and health care costs were halved for the diagnosis and treatment in women with miscarriage and a history of recurrent miscarriage.

Main results and the role of chance: In 2006, 14% of women with a miscarriage were admitted, whereas in 2009 and 2012 none. The surgical management per time period. Actual cost differences with 95% CI were calculated. In addition, a scenario analyses were done using non-parametric bootstrapping.

Wider implications of the findings: By identifying immunologic disorders in patients with recurrent miscarriage targeted therapies might be developed.

Study design, size, duration: Quality of early pregnancy care was measured in women with miscarriage. Whether EP AUs improve early pregnancy care and save costs is largely unknown as stated in the recently published NICE guideline.

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