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2019 FRM MEETING ABSTRACTS

Abstracts presented at the 2019 Foundation for Reproductive Medicine Conference on Translational Reproductive Biology and Clinical Reproductive Endocrinology

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2019 Young Investigator Award Winner

643: Does the CGG repeat size and composition at FMR1 gene explain the unexplained recurrent spontaneous abortion?

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Objective
Recurrent spontaneous abortion is multifactorial disorder and till date various factors have been attributed in its pathogenesis. Still approximately 50% of RSA cases remain unexplained. Premutation (PM) expanded allele of fragile-X mental retardation 1 (FMR1) gene is known to contribute to ovarian dysfunction in 20% of the cases. Recently, link between expanded FMR1 allele and recurrent miscarriages have been reported.
Design
The present case-control study was conducted in women with RSA of Indian origin comparison to age matched healthy control women (N= 100 each) during the period from 2015 to 2019
Materials and Methods
We have investigated the status of CGG repeat size at 5'UTR of the FMR1 gene in all cases and control samples. The genomic DNA from these samples was subjected to molecular analysis for characterization of CGG repeat size and composition at FMR1 gene
Results
As compared to the control women, the RSA women cohort had a higher frequency of carriers with expanded alleles in grey zone (GZ) and PM range i.e. 2% (2/100) verses 5% (5/100) respectively. Also, the RSA cohort had a significantly higher number of normal alleles with ≥35 CGG repeats (24 out of 200 alleles) as compared to control group (8 out 200 alleles). The number of larger FMR1 alleles with pure CGG repeat tract was found to be significantly higher (P= 0.0058) in the RSA group (17 out of 200 alleles) as compared to that in control group (4 out of 200 alleles).
Conclusions
Henceforth, the CGG expanded uninterrupted FMR1 allele might be associated with recurrent abortions and may help to explain many of these unexplained cases.
Support
Funding was received by Council of Scientific and Industrial Research, Lucknow, Government of India.
Disclosure
Authors have no conflict of Interest.

2019 Young Investigator Award 1st Runner-Up

620: Expression and sequencing of genes involved in the pathogenesis of Mayer Rokitansky Kuster Hauser syndrome

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Objective
Uterine and vaginal anomalies occur commonly in women with reproductive dysfunction. Mayer Rokitansky Kuster Hauser syndrome (MRKH), otherwise known as Mullerian Aplasia, falls at the severe end of the spectrum of such anomalies and affects approximately 1 in every 4000 women. This

syndrome manifests itself as the absence of the uterus and/or vagina and may be associated with other anomalies such as kidney, heart, or bone defects. Although a genetic component to MRKH has been suggested, little is known of causative genes. The purpose of this study was to investigate candidate genes and gain a further understanding of the pathogenesis of MRKH and associated anomalies.

Design

This study utilized a cross-sectional approach to examine the genetic framework of a selection of patients currently diagnosed with MRKH as well as relevant family members.

Materials and Methods

The candidate genes being analyzed either came from a list of gene variants stratified during whole exome sequencing (WES) on 14 MRKH trios (1 MRKH proband + 2 family members), 2 duos, and 1 singlet or from close vicinity to breakpoints identified on a balanced chromosomal translocation (3;16) within an MRKH patient. Sanger sequencing was used to confirm likely pathogenic gene variants from WES. Reverse transcriptase-PCR (RT-PCR) was used to test the expression of all 38 genes in MRKH related organ tissue (kidney, heart, and uterus).

Results

DNA Sequencing of variants resulted in 15 of the 17 variants being confirmed, with one unconfirmed, and one in progress. Findings from RT-PCR resulted in 26 of 38 genes showing expression in >1 MRKH dependent tissue with 9 of the other genes still in progress.

Conclusions

Our findings have permitted prioritization of candidate genes that will be considered for sequencing on a larger sample of MRKH patients. Likely pathogenic variants with detrimental effects in vitro that segregate with the phenotype will suggest a role in the pathogenesis of MRKH.

Support

The Medical Scholars Program, Medical College of Georgia, Augusta, GA

Disclosure

None

2019 Young Investigator Award 2nd Runner-Up

616: RNA-SEQ ANALYSIS OF BLASTOCOEL FLUID REVEALS A UNIQUE GENE EXPRESSION SIGNATURE PROFILE IN EUPLOID EMBRYOS THAT SUCCESSFULLY IMPLANT

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Objective

Discovering a molecular signature in day-5 blastocysts that is suggestive for a successful uterine implantation would provide reproductive specialists an additional tool for selecting the very best embryo for transfer. This study assessed global gene expression using RNA-Seq in blastocoel fluid-conditioned media from euploid embryos resulting in (un)successful implantations.

Design

Retrospective analysis of day-5 euploid blastocoel fluid gene expression and implantation outcomes.

Materials and Methods

Blastocoel fluid-conditioned media was obtained following biopsy of ICSI-generated day-5 blastocysts. RNA was extracted and libraries prepared using a SMART-Seq Stranded kit followed by Illumina NextSeq500 sequencing. Sequences were aligned to the human genome, reads counted and gene expression determined. The PANTHER classification system (pantherdb.org) was used to identify signaling pathways most represented in the RNA-Seq gene lists per sample. Embryo implantation-related genes were included in the analysis (Sanchez-Ribas et al.,Fert Steril 2019;111:991).

Results

A greater number of expressed genes (n=1484) were found associated with no euploid implants than embryos (n=778) that did implant. A greater percentage of genes belonging to apoptotic (1.2 vs 0.6%), GnRH (2.4 vs 1.4%), inflammation (3.1 vs 0.8%) and Wnt (2.3 vs 1.5%) signaling pathways were found to be associated with a successful vs unsuccessful implants. These pathways are elevated in the embryo implantation-related genes. The ubiquitin-proteasome signaling pathway had a greater expression percentage in the negative (0.9%) pregnancy outcomes than positive (0.3%) outcomes.

Conclusions

We identified specific gene expression in unique signaling pathways in conditioned media from euploid embryos capable of establishing a successful pregnancy outcome.

Support

UTHSCSA

Disclosure

None

609: The importance of embryo quality and day of biopsy in frozen single euploid blastocyst transfer cycles

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Objective
To verify the most relevant factor in predicting the pregnancy potential of a single euploid blastocyst in frozen embryo transfer (FET) cycles: the blastocyst quality or the day of embryo biopsy.
Design
A retrospective, observational, single center cohort study was carried out between March 2017 and June 2019 (REFA041). Patients who performed a euploid single FET with blastocysts biopsied on Day 5 (D5) or Day 6 (D6) were included. Only the first FET cycle of each patient was considered. Severe male factor and patients with uterine malformations were excluded.
Materials and Methods
Mature oocytes were inseminated by ICSI and/or IVF and normally fertilized oocytes were cultured till day 7. Expanded blastocysts were graded before TE biopsy and inner cell mass (ICM) and trophectoderm (TE) were classified as: A for good, B for fair and C for poor quality, according to Gardner's scoring. Preimplantation genetic testing for aneuploidies (PGT-A) was performed on TE samples by next generation sequencing. Euploid blastocysts were vitrified-warmed and transferred in a natural cycle (NC) or in a hormonal replacement cycle (HRT). Only 331 single euploid FET were included of which 227 were with blastocyst biopsied on D5 and 104 on D6 of women with an average age of 33.9±5.6 years old.
Results
Comparing the fresh cycles characteristics between D5 and D6 FET cycles, no differences were found in maturation (86% vs 85%), fertilization (76% vs 73%), cleavage (98% vs 97%) and euploidy rates (59% vs 58%). No differences were found neither in endometrial preparation (60% vs 52% HRT; 40% vs 48% for NC) nor in endometrial thickness (7.8 ±1.4 vs 7.9±1.6 mm) for D5 and D6 FET cycles. More blastocysts with ICM and TE grade A were transferred on D5 compared to D6 FET cycles (27% vs 17% for ICM; $p<0.001$ and 29% vs 15% for TE; $p<0.001$), however, pregnancy (70.9% vs 64.4%) and miscarriage rates (5.7% vs 6.7%) were not significantly different. Univariate analysis showed an effect of embryo quality on pregnancy rates ($p<0.001$) compared to the day of biopsy ($p=0.203$). A multivariate regression controlling for confounding factors demonstrated that TE quality had a relevant impact on pregnancy outcomes rather than the ICM. Compared to the grade A TE, the adjusted OR was 0.454 for B and 0.429 for C ($p=0.028$).
Conclusions
Higher TE quality increases pregnancy rates irrespective of the day at which blastocyst biopsy is performed.
Support
None
Disclosure
None

623: Fragile X carrier investigation and Genetic counselling of Premature ovarian insufficiency females in an Indian scenario

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Objective
Fragile X-associated primary ovarian insufficiency (FXPOI), a type of ovarian dysfunction is caused by premutation (PM) expansion mutation (55-200 CGG repeats) in FMR1 gene. It occurs in ~20% of PM females carriers. The risk of having FXPOI in PM female increase with the increase in the number of CGG repeats and is maximum at 80 CGG repeats. Furthermore, 2-6% of women with isolated POI or 14% of women with familial POI are reported to be PM carriers. About 12.6% of women with FXPOI are reported to conceive spontaneously even years after diagnosis. There by suggesting screening of POI females for their CGG repeat expansion status in order to rule out PM as a cause of infertility due to their inherent 50% risk of having Fragile X syndrome (FXS) affected offspring. The study aims for the molecular screening of females POI cohort for presence of PM expanded FMR1 alleles.
Design
Two hundred POI cases were recruited from the Department of Medical Genetics, SGPGIMS, Lucknow, India during the period from 2015 to 2019.
Materials and Methods
A previously validated laboratory-developed test using triplet-primed polymerase chain reaction (TP-PCR) was used to identify PM alleles in POI females. Genomic DNA was extracted from 200 POI females and subjected to TP- PCR amplification. The amplicons were subjected to fragment analyses and results were documented. Genetic counseling and extended family screening was offered to identified PM positive cases.
Results
Triple-primed- polymerase chain reaction (TP-PCR) screening of 200 POI females identified 5 of 200 subjects with (Grey zone) GZ allele and 7 subjects with PM allele. Genetic counselling and extended family screening was done in carriers.

Conclusions
The frequency of PM carriers identified in this study was significant and in concordance with previous studies carried worldwide. PM carrier identification among POI subjects will serve dual purpose of recognizing cause for ovarian dysfunction and in getting genetic counselling that will help carriers in taking reproductive decisions.
Support
Funding was received by Intramural Project grants, SGPGIMS, Lucknow of India, Government of India
Disclosure
Authors have no conflict of Interest.

642: Molecular screening for FMR1 expanded allele in Indian females for fragile X carrier detection

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Objective
Premutation (PM) carriers are reported to be more frequent in population in comparison to FM (Full mutation) with a frequency as high as 1 in 113–259 women and are unstably transmitted to the offspring as FM, when passed onto offspring through female. In spite of a high frequency of PM carriers and its known risk of expanding to FM in subsequent generation, most PM carriers are unaware of their condition. Thus depicting the importance of tracing potent women PM carriers in order to decrease the disease load in the society. The main objective of the study is molecular screening of females of reproductive age for presence of PM expanded FMR1 (Fragile X mental Retardation 1) alleles.
Design
The study was conducted in 500 reproductive age females of Indian origin and extended family screening will also be offered to identified PM positive cases during the period from 2015 to 2019.
Materials and Methods
A previously validated laboratory-developed test using triplet-primed polymerase chain reaction (TP-PCR) was used to identify PM alleles in 500 Indian reproductive age females.
Results
We identified 2 (0.4%) asymptomatic PM and 1.6% (8/500) GZ (grey zone) carrier females in reproductive age cohort. Extended family screening was possible for 4 of 8 (60%) GZ and for both (100%) PM females.
Conclusions
In spite of clinical significance of conducting screening program for identification of the carrier status of reproductive age women, such objective had greatly suffered due to unavailability of accurate, cost effective and rapid molecular techniques. The indigenously developed TP-PCR in our study is cheaper and in comparison to available commercial kits and thus it has proved to be economically more feasible to be used in screening program.
Support
Funding was received by Intramural Project grants, SGPGIMS, Lucknow of India, Government of India
Disclosure
Authors have no conflict of Interest

617: Effect of intrauterine and lactation exposure to nicotine on oocyte quality of adult rats

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Objective
This work aimed to verify the quality of the female gametes of rat offspring exposed to nicotine during intrauterine and lactation phases.
Design
The gonadal development begins in the intrauterine phase and women are born with an established oocyte reserve. Exposure to drugs during gestation can compromise the offspring health, which includes loss of quality of the gametes. Nicotine (main component of cigarettes) is a potent pro-oxidant, able to alter fertility of men and women. As oocytes are susceptible to oxidative stress, this drug can cause damage to cellular membrane, changes in oocyte maturation and may induce errors during chromosome segregation. Besides, it can cause increase of oocyte DNA fragmentation. The oocyte mitochondria are susceptible to injuries, which may affect oocyte quality and future embryo development. Thus, considering the high number of women who smoke during pregnancy and the importance of the events that take place in the embryonic development for future offspring fertility, our group has been studying the gametes quality of rats progenies from dams exposed to nicotine.
Materials and Methods
For this purpose, 10 pregnant and lactating rats received nicotine through an osmotic minipump (2mg/kg/day), mimicking human moderate cigarette consumption (nicotine group). Other 10 rats received the minipump implant without nicotine (control group). The oocytes were analyzed for viability (propidium iodide), level of lipid peroxidation (BODIPY), mitochondrial function (MitoTracker) and generation of reactive oxygen species (Cellular Reactive Oxygen Species Detection Assay Kit) when the female offspring were 90 days-old. The results were submitted to statistical analyses

using SigmaPlot Software. Test t were applied for parametrical and Man Whitney for non-parametrical parameters (p≤0,05).

Results

Although oocyte mitochondria from nicotine group showed reduced activity (5667.65) when compared to control group (8249.32), no statistical differences between groups for all fluorescent labeling parameters performed were found.

Conclusions

Nicotine seems not to have a negative effect on oocyte after exposure during pregnancy and breastfeeding. However, other analyzes are being conducted to evaluate the DNA quality of these oocytes.

Support

São Paulo Research Foundation (FAPESP 2017/06668-4)

Disclosure

None

618: A Case Series of Prednisolone to Treat Unexplained Recurrent Miscarriage

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Objective

Unexplained recurrent miscarriage is a devastating condition, occurring in up to 50% of cases of recurrent miscarriage. It has been suggested that relative glucocorticoid deficiency in the endometrial stroma could impair decidualisation, leading to recurrent miscarriage, therefore treatment with prednisolone has been proposed as an option. The objective of this study was to examine the outcomes of treatment of unexplained recurrent miscarriage with prednisolone.

Design

A retrospective review of 54 cases of unexplained recurrent miscarriage treated with prednisolone was conducted.

Materials and Methods

All patients treated with prednisolone were identified and a retrospective computerised casenotes review was conducted. The primary outcomes were livebirth after 24 weeks, the secondary outcomes were complications associated with prednisolone including intrauterine growth restriction and fetal anomalies including cleft palate.

Results

42 patients with 54 pregnancies were commenced on a prednisolone regime until 12 weeks of pregnancy. 20mg of prednisolone was given from a positive pregnancy test which was tapered from 10 weeks and stopped at 12 weeks. The mean age of the patients was 36. All patients had previous recurrent pregnancy losses ranging from 2-9. Patients were given therapy with cyclogest pessaries, high dose folic acid and prednisolone. 64% of cases resulted in a livebirth > 24 weeks. 9 cases are currently an ongoing pregnancy. There were 26 live children (including 1 set of monochorionic diamniotic twins), 11 early miscarriages, 2 pregnancies of unknown location and 1 pregnancy loss at 22 weeks due to preterm premature rupture of membranes at 17 weeks. There were 2 cases of intrauterine growth restriction. There were 4 preterm births. There were no fetal anomalies including cleft palate.

Conclusions

Sixty four percent of patients with unexplained recurrent miscarriage had live birth following treatment with prednisolone until 12 weeks of pregnancy. Prednisolone appears to be a safe treatment option for the management of recurrent miscarriage. A large randomised control trial of prednisolone use in unexplained recurrent miscarriage is required to further assess its benefit.

Support

None

Disclosure

None

644: Instillation of Intraovarian Platelet Rich Plasma for enhancing Reproductive outcome: The Jaslok Experience

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Objective

To evaluate improved reproductive potential utilising intraovarian PRP in women with POR, DOR, low AMH, low AFC.

Design

Prospective observational study in Indian women visiting our centre.

Materials and Methods

1. Women with POR, DOR, low AMH (<1.49 ng/ml), diminished antral follicle count </= 6(n=27), poor responders. 2. Age group 29-43 average age: 36yr. 3. Women with menstrual cycles. Informed consent was obtained from the woman undergoing the intraovarian PRP instillation procedure. IRB and Ethics Committee approval was obtained. Preparation and Instillation of PRP: Plasma is separated by centrifugation of 60 ml of blood. Platelet Rich Plasma (PRP) is frozen in liquid nitrogen in small aliquots. The woman undergoes mild or

standard ovarian stimulation. At the time of oocyte retrieval or follicular aspiration, 1ml of prepared PRP is instilled via transvaginal ultrasound into the aspirated follicle(s). Instillation of 1 ml of PRP becomes easier when the ovary is mildly stimulated as 1 ml can be accommodated in the follicle. The instillation is to be repeated over 3 cycles.

Results

The end point of the study is: 1) Better quality and quantity of oocytes and embryos to establish pregnancy; 2) Establishment of pregnancy. Of the 27 women who underwent PRP, 25 have yet to complete the 3 cycles of instillation. Of the 27 women, 22 have completed 1 instillation, 2 have completed 2 instillations and 3 have completed 3 instillations. 1 woman aged 29 yrs with an AMH of 1.5ng/ml showed a significant improvement in the quality of embryos as compared to her previous 2 cycles of IVF. She conceived by IVF after completing the instillations and is currently 12 weeks pregnant. 1 woman aged 36 yrs who had undergone 10 failed cycles of IVF, underwent 1 PRP instillation and conceived naturally 3 months later, Of the 27 women, 7 underwent IVF post the PRP instillation, the rest are awaiting completion of 3 instillations. Out of 27 women, 3 are lost to follow up, 2 have completed 3 instillations and others are ongoing.

Conclusions

Although this is a small study, the limited success with this technique is encouraging. This study is a step towards enhancing fertility success rates in women with very few options for pregnancy.

Support

None

Disclosure

None

648: Women with endometrial factor benefit from platelet rich plasma instillation

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Objective

To record the improvement in the endometrial lining and pregnancy rates in FET cycles of women following intrauterine Platelet Rich Plasma (PRP) instillation.

Design

This is an ongoing study from August 2018 to July 2019 at our center. Women in the age group of 25 to 45 years with a history of previous failed cycles or cancelled cycles or those with thin endometrial lining were included.

Materials and Methods

212 women undergoing FET at our center were included in the study. Following their consent Intrauterine instillation of approximately 1 ml of autologous PRP was carried out on day 5, day 12 of endometrial priming and 48 hours prior to embryo transfer. The endometrial thickness was evaluated by Transvaginal Ultrasound on days of PRP instillation and embryo transfer. 11 women did not undergo embryo transfer due to non-improvement of the uterine lining. The Bhcg test was done 14 days after the embryo transfer.

Results

180 out of 201 women showed significant improvement in the endometrial lining. Of 201 women in the study, 66 women conceived (33%). Of these women, 34 had never conceived in the past. Of the 66 pregnancies following PRP instillation, 12 women had miscarriages (18%) and 51 are ongoing pregnancies. There were 8 biochemical pregnancies (12%). 41 women had past history of Genital TB. Of these 41 women with genital TB, 16 (39%) got pregnant. Of the 16 pregnancies with a history of genital TB, 12 are ongoing pregnancies and 4 miscarried.

Conclusions

Intrauterine infusion of PRP has a potential to improve the endometrial lining and clinical pregnancy rates in women with multiple failed attempts and also holds promise for women with a past history of genital TB where traditionally, implantation rates are low.

Support

None

Disclosure

None

604: Establishment of in vitro culture condition for ovarian primordial follicles

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Objective

A decrease in the number of hormone-responsive follicles) is a hurdle for infertility treatment. According to women's aging, these follicles are decreased but the primordial follicles still remain. Primordial follicles are non-responsive to gonadotropins, therefore, women with diminished ovarian reserve (e.g. age factor, POI, cancer survivor, poor responder) are not ideal for current therapeutic strategy.

Design
In this study, we tried to establish in vitro culture condition of primordial follicles using a mouse model.
Materials and Methods
Ovaries of two-week-old C57BL/6 female mice were collected and dissociated into single follicles mechanically. Isolated, single primordial follicles were cultured in media drop covered with mineral oil. The media consisted of either MEMα or DMEM/F12 supplemented with bFGF. After 14 days of in vitro culture, the seeded follicles expanded to the secondary follicles then 200 IU/L FSH (Gonal-F), 100 IU/L LH (Luveris) were added. At day 20, the follicles were matured and the ovulation was induced by treatment with hCG and EGF. Distribution of tubulin was confirmed by immunostaining and the expression of Figla and Nobox was evaluated by qRT-PCR.
Results
In vitro development of primordial follicles was achieved with a higher efficiency in the group MEMα. The ovulation rate of in vitro developed oocytes was 20% and 8%, respectively. The ovulated oocytes were at M II stage and the cytoskeletal structure demonstrated normal distribution. The primordial follicle-derived oocytes expressed oocyte development-related genes, Figla and Nobox, as compatible to naturally developed oocytes.
Conclusions
Taken together, we established in vitro culture condition of primordial follicles using paracrine factors. The condition should be further optimized in order to get a higher efficiency. The fertile ability of primordial follicle-derived oocytes should be confirmed in the future.
Support
2016R1D1A1B03934784 and 2016R1E1A1A01943455
Disclosure
None

593: Metformin Ameliorates Endometrial Receptivity of Minimal/mild Endometriosis

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Objective
Endometriosis reduce female fecundity, most of endometriosis-associated infertility was minimal or mild endometriosis according to r-AFS score. The decreased endometrial receptivity should be responsible for the pathogenesis. Metformin inhibited the growth of ectopic loci. However, the affect of Metformin on eutopic endometrium of minimal/mild endometriosis had not been reported. This study aims to identify whether metformin can ameliorate eutopic endometrial receptivity in infertile women with minimal/mild endometriosis.
Design
This is a controlled trial to compare protein expression of eutopic endometrium of minimal/mild endometriosis patients after 2 months treatment of Metformin (1000mg/d).
Materials and Methods
Total of 10 infertile women with minimal/mild endometriosis diagnosed laparoscopic were enrolled into the study, their secretory phase endometrium (10 pairs) were collected by simultaneously hysteroscopic curettage and Pipelle (Endometrial Suction Curette) after 2 months Metformin therapy (1000mg/d) (5 cases) or controls (5 cases). Protein expressions of eutopic endometrial tissues were analyzed by liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) based proteomics.
Results
A total of 20 endometrial samples were analyzed. Compared to baseline, 149 differentially expressed proteins were detected in the endometrium after metformin therapy. Some transforming factors related with endometrial receptivity like insulin-like growth factor-binding protein 7 (IGFBP-7), α-antitrypsin (AAT), apolipoprotein D (ApoD), Rho GDP-dissociation inhibitor 1 (Rho-GDI), brain form glycogen phosphorylase (PYGB) and Cathepsin B had up-regulated after metformin therapy ($P<0.05$); while the expressions of those protein had no significant change in controls.
Conclusions
Our trials revealed that metformin, an insulin sensitizer, may ameliorate endometrial receptivity of eutopic endometrium of minimal/mild endometriosis in molecular aspects, that could be used as potentially novel therapy to improve the fecundity of infertile women with minimal/mild endometriosis.
Support
None
Disclosure
None

590: HUMAN GROWTH HORMONE COUPLED WITH THE CMAP ACUPUNCTURE PROTOCOL (GH-CMAP) ENHANCES BLASTOCYST FORMATION AND CLINICAL PREGNANCY RATES

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Objective
The aim of this study was to evaluate supplemental HGH both before and during ovarian stimulation coupled with the

Cridennda Magarelli Acupuncture Protocol (CMAP) (GH-CMAP Protocol) in terms of oocyte retrieved, oocyte maturity, blast formation, and clinical pregnancy rates.

Design

This is a preliminary, prospective cohort study conducted in 2018 on 112 patients, including GH-CMAP (48) vs. antagonist protocol (A) group (64) (control).

Materials and Methods

A regular antagonist protocol with 1.6mg/day HGH was given (n=48) before and during antagonist stimulation (AS) period; 64 patients were undergoing regular AS protocol (2017-2018). The CMAP protocol (3) was used with supplemental estrace, DHEA, CoQ10. Duration of ovarian stimulation GH-CMAP averaged 10 days, the control group 11 days. Normality of all variables was evaluated and number of oocyte, oocyte maturity rate and blast formation rate were log 10 transformed to become normal distribution. Multivariate regression model (JMP version 14.0) was performed to assess the effect of GH-CMAP on number of oocytes retrieved, oocyte maturity rate and blastocyst formation rate, adjusted by independent variables including age, AMH, BMI, FSH. Total number of patients N=112; GH-CMAP group n=48; Antagonist group n=64;

Results

Co-stimulation with HGH in the GH-CMAP protocol improved blast formation rate (GH-CMAP 1.75±0.05, A 1.59 ±0.03; p=0.0252). Pregnancy rates trended higher in GH-CMAP group (58.8%) than in the AS protocol group (46.6%). Fewer number of oocytes retrieved (GH-CMAP 9; A13; p=0.0095) and lower oocyte maturity rate (p=0.1397) was observed in GH-CMAP group by design. There was a statistically significant association between BMI and blastocyst formation rate in that the higher BMI, the lower blastocyst formation rate (p=0.0085).

Conclusions

These data provide evidence that the positive effect of GH-CMAP on blast formation, consequently improve clinical pregnancy rate. The implantation rate and live birth rate are needed to be included in the further study. These results need to be confirmed by a large-scale randomized controlled trial.

Support

None

Disclosure

None

601: is there still a place for andrological examination, lifestyle modification, associated with antioxidant treatment, in the management of male infertility in couples waiting for artificial insemination

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Objective

In one hand, advances in assisted reproduction technologies (ART) have significantly reduced the importance of male clinical evaluation. Subfertile men are often referred to ART only on the basis of a spermogram, without andrological examination. In the other hand, systematic review of observational studies has shown that medical or surgical treatment, as well as modifiable clinical lifestyle factors can thus, sufficiently improve the quality of spermatozoa so as to reduce the need for assisted procreation (from IVF to IUI) or to avoid it altogether.

Design

Retrospective study between January 2018 and December 2018. From the total cohort of 443 infertile couples referred for IntraUterine Insemination to the ART unit of our hospital.

Materials and Methods

443 men underwent andrological examination, followed a Mediterranean diet, taken an oral antioxidant supplementation. Hypofertile men were controlled every three months with a spermogram. Data was analyzed by the hospital biostatistics department. The outcomes were evaluation of sperm parameters and spontaneous pregnancy (with live birth, follow-up period of 2 years).

Results

After treatment, the mean spermatozoid concentration and motility were significantly increased, respectively from 6.8 to 14.6 ×106 spermatozoids /ml and 14.4 to 27, 4 %. Spontaneous pregnancy was observed in 115 couples (26%). Concerning the couples who had no pregnancies (284), 38 % showed increase of sperm parameters, which allowed them to change the expected IVF by Intra Uterine Insemination (followed by 13 % pregnancy).

Conclusions

The preliminary results of our work are in agreement with the recent observational studies on this subject. oral antioxidant supplementation, as well as modifiable clinical lifestyle factors, have beneficial effects on male fertility parameters and fecundability. It would be more interesting to have a larger patient population over a longer period, with a more in-depth analysis of the therapeutic effects. Andrological examination should be systematic, in an attempt to identify potentially treatable pathology before engaging in ART. Advances in ART should complement the evaluation and treatment of the male partner, not replace it.

Support

None

Disclosure

None

652: Could couples with mild male factor infertility and at least 3 failed previous IVF attempts benefit from laparoscopic investigation

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Objective
To assess the value of laparoscopy for couples diagnosed with mild male factor infertility and at least three previous failed In-Vitro Fertilization (IVF) attempts.
Design
Prospective cohort study.
Materials and Methods
A total of 169 couples participated in the study. One-hundred and one couples underwent laparoscopic investigation and correction of previously unidentified endometriosis or pelvic adhesions. The main outcome measures were live Birth/ Ongoing Pregnancy rate, clinical pregnancy rate and positive hCG rate.
Results
One-hundred and sixty-nine women were presented with the option of laparoscopic investigation. One-hundred and one of them opted for, whereas 68 opted against laparoscopy performance. All patients proceeded with a single ICSI cycle. Following laparoscopic investigation, 43 patients were diagnosed with endometriosis, 22 with adhesions, while for 36 laparoscopic investigation provided no further diagnosis. No statistically significant differences were observed regarding the baseline hormonal levels and other characteristics between the two groups and the three subgroups. When compared to the no-laparoscopy group, women subjected to laparoscopy presented with a higher clinical pregnancy and ongoing pregnancy/live birth rate. Following endometriosis correction, a marginally non statistically significant trend was observed regarding a decrease in poor-quality blastocysts (p=0.056). A statistically significant higher clinical pregnancy (p=0.03) and ongoing pregnancy/live birth rate was observed in the endometriosi
Conclusions
Laparoscopic identification and correction of undiagnosed endometriosis in couples initially diagnosed with male infertility and at least 3 failed previous IVF attempts, appears to be a promising approach efficiently addressing infertility for these patients while avoiding IVF overuse.

Support
None
Disclosure
None

637: The effect of Genital TB in Indian women on Endometrial Receptivity Status

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Objective
Chronic Endometritis (CE) is a frequent cause of implantation failure. In India, the most common cause of CE is Genital Tuberculosis (TB). The aim of this study was to determine if there was a higher incidence of a non receptive endometrium by Endometrial Receptivity Analysis (ERA) in women with a past or present history of Genital TB. The secondary objective was to show if there was a difference in pregnancy rates of women with past or present history of Genital TB among the receptive and non receptive status groups.
Design
Retrospective observational study in Indian women visiting our Fertility Centre.
Materials and Methods
Over a 2 year period, 273 women of Indian ethnicity visiting our fertility clinic with a high suspicion for Genital TB underwent the ERA test for endometrial receptivity. Criteria for the diagnosis of Genital TB were one or more of the following. Blood test for Gamma Interferon, ESR, Mantoux test, Endometrial Biopsy for TB PCR, Histopathology, TB culture and Immunohistocytochemistry, Laparoscopy, Hysteroscopy and Ultrasonography. The endometrial receptivity status was diagnosed by the Endometrium Receptivity Analysis (ERA) test using the Next Generation Sequencing (NGS) platform.
Results
Of the 273 women, 91 (33%) had a nonreceptive endometrium and 182 (67%) had a receptive endometrium. Of the 182 women with receptive endometrium 67 (37%) had a history of TB, Latent TB or Active TB. Out of 91 women with nonreceptive endometrium 53 (58%) had a history of TB, Latent TB or Active TB. Of these 53 women with nonreceptive status 52 (98%) had a prereceptive endometrium and only 1 (2%) had a post receptive endometrium. Out of the 120 women with history of TB, Latent TB or Active TB, 53 (44%) were non receptive.

Conclusions
Our study found a higher incidence of nonreceptive prereceptive endometrium in those affected by Genital TB. This may be explained by the destruction of the progesterone receptors in the functional epithelium of the endometrium due to its atrophy apoptosis of cells and fibrosis.
Support
None
Disclosure
None for Firuza.R.Parikh, Madhavi Panpalia, Trupti Mehta, Sujatha Sawkar, Anahita Pandole, Sangeeta Deshmukh, Sapna Agarwal, Mamta Katakdhond, Chitralekha Ishwar, Havovi Presswalla, Jyotshna Palgamkar, Meenal Khandeparkar

647: The use of Artificial Intelligence (AI) in interpreting the validity of mitoscore

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Objective
Other than providing vital information about the euploid status of an embryo, NGS also provides key information about the nuclear and mitochondrial genome ratio, commonly referred to as Mitoscore. Although there is no consensus regarding the predictability of Mitoscore for the range of implantation efficacy and is variable across the globe, our objective was to evaluate Artificial Intelligence (AI) and R based prediction for an acceptable range of mitoscore.
Design
Retrospective cohort study.
Materials and Methods
Written consent of couples undergoing PGT was obtained. Embryos were biopsied and taken up for NGS. Trophectoderm biopsy leading to 3-6 cell source was subjected to whole genome amplification followed by library preparation followed by NGS for 1000 embryos. Chromosomal aneuploidy data and ratio of nuclear to mitochondrial genome were subjected to R based machine learning and deep learning. Observed data and predicted data were compared using biostatistics for evaluating positive prediction efficacy of mitoscore and its correlation with clinical outcome. The data of 1000 embryos were subjected to deep learning and machine learning algorithms like random forest, support vector machine, general linear model and linear discriminant analysis. Open source software package like h20 R package was employed to perform R analysis and Box-Behnken design (BBD) using response surface methodology (RSM).
Results
NGS data revealed 100% chromosomal aneuploidy, in embryos with mitoscore above 40 and 92.86% embryos were abnormal when mitoscore was observed to be less than 25. R2 analysis also predicted with confidence interval of 0.9843 that mitoscores above 40 and less than 25 were predictive of aneuploidy in any one/multiple chromosomes. Clinical outcome was positively correlated with embryos having mitoscore between 25 to 40, which was positively predicted by machine DOE and R2 analysis with 0.9769 confidence.
Conclusions
Thus from the experimental data, R package prediction through deep learning and machine learning, it can be concluded that Mitoscore can be reliably employed as a selective biomarker for implantation efficacy of euploid embryos.
Support
None
Disclosure
None

630: Metabolic effects of short–term whey protein supplementation in polycystic ovary syndrome

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Objective
This study evaluated the effects of short–term whey protein ingestion on incretins and glycemic regulation in women with and without polycystic ovary syndrome (PCOS and CON respectively).
Design
Repeated measures design with convenience sampling method was used. Twenty-nine young, body mass index- matched women (PCOS=14 and CON=15) underwent 150-min oral glucose tolerance test (OGTT) without protein preload (Day 0) followed by tests on the first and last days of 1-wk supplementation (Days 1 and 7 respectively). Subjects ingested 35g whey protein per day. Eight venous blood samples were collected during each test to assess levels of glucose, insulin, active glucagon-like peptide 1 (aGLP-1) and total glucose-dependent insulinotropic polypeptide (tGIP).

Materials and Methods
Multiplex assays was used for quantification of tGIP and aGLP-1. Insulin concentrations were analyzed using ELISA. Repeated measures ANOVA with Bonferroni post hoc tests were used to compare the effects of PCOS status, time, Day and their interactions on glucose and hormone levels. P-value ≤ .05 was considered significant.
Results
In both groups, postprandial changes in glucose levels were significantly lower on Days 1 and 7 compared to Day 0 ($p<.05$). Preloading also increased insulin levels ($p<.05$; Day 0=55.2 vs Day 1=69.9 vs Day 7=84.8 μIU/ml). Day, time ($p<.05$), and time x group ($p=.04$) interactions significantly affected insulin responses. In both groups insulin increased successively on Days 1 and 7 compared to Day 0 (Day 0=55.2 vs Day 1=69.9 and Day 7=84.8 μIU/ml). During all OGTTs CON group had higher aggregated tGIP levels compared to PCOS group ($p = .04$; 322 vs 234.8 pg/ml) whereas aGLP-1 increased significantly on days of preloading compared to Day 0 ($p = .03$) in both groups.
Conclusions
A 35g whey bolus before the glucose load enhanced insulin release and consequently lowered circulating glucose in women with and without PCOS. The insulinogenic effect of preloading can be attributed to higher aGLP-1 levels. Women without PCOS exhibited notably sustained and greater glycemic control in response to short–term protein supplementation compared to women with PCOS. The study concludes that the incretin mimetic effect of whey may aid women with PCOS in achieving glycemic homeostasis and reducing risk of type 2 diabetes mellitus.
Support
TWU REP; Glanbia LLC
Disclosure
None

649: Cap Score Utility in Treatment of Varicocele Associated MalRetrospective analysis: Cap-Score, and SA metrics were compared in 7 men before and at least three months after varicocelectomy e Infertility

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Objective
Varicocele is a known cause of male infertility. Improvement after varicocelectomy is often assessed by changes in semen analysis (SA). However SA lacks a functional test of fertilizing ability. Cap-Score™, which reports the percentage of sperm that can capacitate, functionally assesses male fertility and can prospectively predict pregnancy. In this study, we examined the effect of varicocelectomy on SA, and Cap-Score, and then applied results to post procedure counseling.
Design
Retrospective analysis: Cap-Score, and SA metrics were compared in 7 men before and at least three months after varicocelectomy
Materials and Methods
Semen specimens for analysis were collected and assessed according to WHO 5th Edition guidelines. Volume, concentration, motility and morphology were assessed in a single facility. With respect to Cap-Score, fixed samples were initially processed on site and then sent to Androvia LifeSciences for Cap-Score determination.
Results
After varicocelectomy, 71% (5/7) men had a significant increase in Cap-Score; average increase was 12.6 ± 1.0%. 2 men had an insignificant change. Significance in improvement was assessed by paired samples t-test ($p=0.02$). With respect to semen analysis, 3 men had improvement in sperm concentration, motility and morphology, 1 in motility and morphology, 1 in concentration and morphology, and one in morphology only. Overall, 6/7 men (86%) had some improvement in semen parameters.
Conclusions
In this limited sample, 5 (71%) of men who underwent varicocelectomy had significant improvement in Cap-Score. This corresponded to a 91% increase, from 23 to 44%, almost doubling the probability of generating a pregnancy over three cycles, as predicted by Cap-Score sperm function assay. These men were encouraged to pursue conservative options including natural conception and or IUI. Whereas the 2 men who did not have a significant change were advised to pursue IVF-ICSI, including one of the men who had improvement in semen parameters. Cap-Score can both serve as an independent indicator of the need for treatment and also can stratify post procedure care in the setting of male infertility diagnosis and therapy.
Support
None
Disclosure
None

651: Assessing the practice of LuPOR for poor responders: a prospective study evaluating follicular fluid cfDNA levels during natural IVF cycles

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Objective
This study aims to assess the practice of luteal phase oocyte retrieval (LuPOR) for poor responders, employing evaluation of cell-free DNA in follicular fluid (ff cfDNA) during natural Assisted Reproduction Technology cycles.
Design
A prospective study enrolling patients based on strict eligibility criteria. The levels of ff cfDNA resulting from follicular phase oocyte retrieval (FoPOR) and LuPOR in a single menstrual cycle were associated with the number and maturation status of yielded oocytes, and the number of resulting zygotes following ICSI.
Materials and Methods
A total of 47 women classified as poor responders based on Bologna criteria were detected with a second luteal phase follicular wave. Follicular fluid was collected and prepared for cfDNA extraction. Levels of cfDNA were quantified via real-time PCR employing sets of ALU115 and ALU247 primers. Both primers are associated with necrotic and apoptotic events that are examined employing the ratio Q247/Q115 representing DNA integrity. Statistical analysis was performed using R statistical programming language.
Results
The mean levels of ALU115 were statistically significantly lower during FoPOR when compared to LuPOR (0.79±0.72 vs 1.46±1.59 ng/μl, p=0.02). Regarding the FoPOR group, a statistically significant positive correlation of serum estradiol levels and ALU115 concentration (p=0.04) was revealed. Finally, a statistically significant lower number of retrieved (1.29±0.58 vs 1.09±0.28, p=0.02) and MII oocytes (0.77 ±0.55 vs 1.08±0.61, p=0.02) was observed when comparing the FoPOR to LuPOR group.
Conclusions
LuPOR reassuringly does not seem to be associated with necrotic events. This study uniquely highlights an aspect of the physiology involved regarding the novel practice of LuPOR, rendering it as a promising approach for poor responders.
Support
M.Sc. Program “Research in Female Reproduction” of the Medical School of Athens.

Disclosure
None

600: Blastocysts with disproportionally high mitochondrial DNA copy number can result in healthy babies

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Objective
To confirm or refute previous claims that mitochondrial DNA (mtDNA) quantitation should be used to rank embryos for transfer in the clinic because blastocysts with high mtDNA copy number invariably fail to implant.
Design
Guidelines have been proposed to increase technical uniformity of mtDNA quantitation across centers from blastocyst-stage biopsies (Wells, Fertil Steril, 2017). Here, we adhere to those guidelines in analyzing mtDNA copy number in 109 blastocysts used for transfer in a single-clinic setting, to determine whether it is a valid predictor of implantation and birth.
Materials and Methods
Levels of mtDNA were quantified in surplus product of the PGT-A process from blastocysts used in IVF with known outcomes. We used qPCR measuring a locus in the mtDNA sequence and a multicopy locus in the nuclear DNA sequence, and computed the ratio between the two values. Statistical comparison between implanted and not implanted groups was performed with a two-tailed unpaired t test.
Results
Blastocysts with extremely high mtDNA levels successfully implanted and led to births. Clinical follow-up of five babies with highest mtDNA levels out of the 109 analyzed blastocysts indicated they were healthy at birth and normal for a panel of 63 screened conditions, including various metabolic disorders. If using mtDNA copy number to deselect embryos, these samples would not have been chosen for transfer, precluding the birth of five healthy babies. In addition, compiled analysis of the 109 blastocysts showed a statistically insignificant difference between mtDNA levels in implanted versus non-implanted blastocysts (average implanted=0.00617,

stdev=0.00447, n=55; average not implanted=0.00528, stdev=0.00305, n=54; P=0.231, ns).

Conclusions

The measurement of mtDNA copy number at the blastocyst stage might not provide any advantage to embryo ranking, and could lead to de-selection of blastocysts that result in healthy pregnancies and births. We conclude that the practice of mtDNA quantitation requires further investigation and validation, and consider the commercial push to implement this test in the clinic premature.

Support

None.

Disclosure

None.

603: Dual triggering with urinary and recombinant gonadotropin-releasing hormone agonist in fresh autologous IVF/ICSI cycles – Is it a matter of timinig?

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Objective

Triggering the final oocyte maturation is one of the most critical steps during in vitro fertilization (IVF) treatment. To reduce the incidence of ovarian hyperstimulation, the dual-trigger system with gonadotropin-releasing hormone agonist (GnRH-a) in addition to a reduced dose of human chorionic gonadotropin (hCG) was invented. However, the debate of the necessity and timing of dual trigger remains controversially discussed. This study was set up to investigate the influence of dual trigger timing within fresh autologous cycles.

Design

Retrospective study

Materials and Methods

Data from 649 cycles of 493 patients were collected from November 2016 to December 2018. Only patients < 40 years and normal responders (AMH > 1.2 ng/ml; FSH < 12 mIU/ml) were included. 311 patients received 5000 IU of urinary hCG (Pregnyl; Organon) in combination with 0.2 mg GnRH-a (Decapeptyl; Ferring Pharmaceuticals) while 182 patients received 6500 IU of recombinant hCG (Ovitrelle; Merck Serrono) in combination with 0.2 mg GnRH-a (Decapeptyl; Ferring Pharmaceuticals). The timing of GnRH-a administration was either 2 or 6 hours before hCG administration, according to the number of immature oocytes in previous IVF cycles. Differences in pregnancy rates and fetal heartbeat rates were evaluated.

Results

A positive beta-hCG was achieved in 29.66% (urinary hCG + GnRH-a) and 31.16% (recombinant hCG + GnRH-a), respectively. Looking at the different time points of GnRH-a administration urinary hCG + GnRH-a (2h) revealed a pregnancy rate of 30.96% while administration of urinary hCG + GnRH-a (6h) revealed a pregnancy rate of 23.94%. In addition, recombinant hCG + GnRH-a (2h) showed a pregnancy rate of 33.06% while the administration of GnRH-a (6h) revealed a pregnancy rate of 27.03%. All comparisons did not show statistically significant differences between groups. Additionally, the number of fetal heart beats was equal between groups.

Conclusions

In conclusion the results of this study show that the timing of GnRH-a administration leads to equal pregnancy and fetal heartbeat rates. Hence it is tempting to speculate that the timing of GnRH-a administration is not a critical factor in triggering final oocyte maturation, which point to more flexibility in reproductive medicine treatment.

Support

None

Disclosure

None