ORGANIZED BY

Scientific Society of Research in Human Reproduction

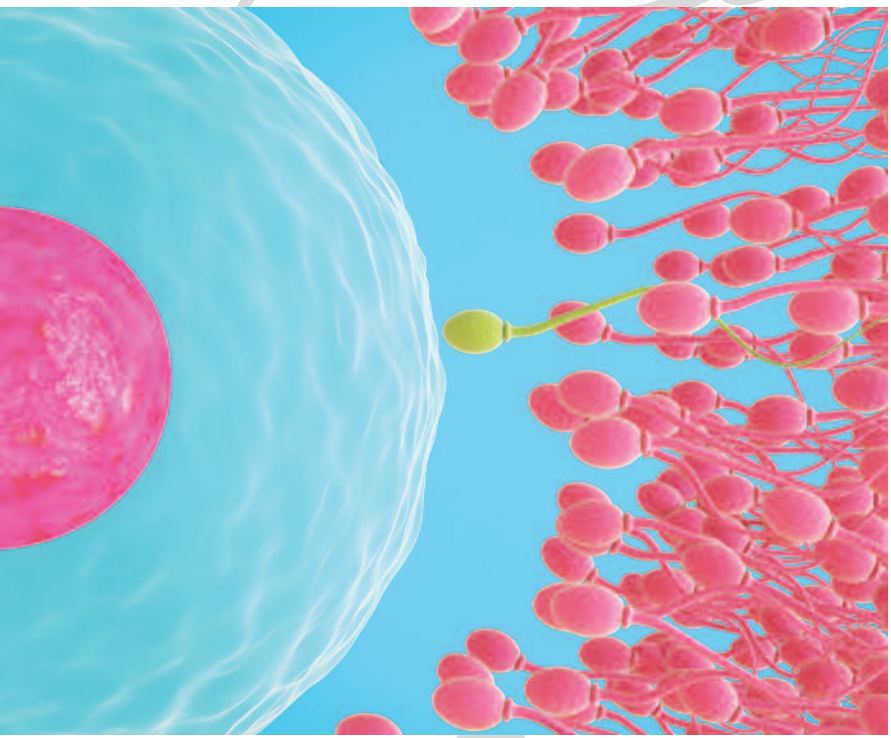
UNDER THE AUSPICES OF

UNIVERSITY OF CRETE
SCHOOL OF MEDICINE

ΕΛΛΗΝΙΚΗ ΜΑΙΕΥΤΙΚΗ ΚΑΙ ΓΥΝΑΙΚΟΛΟΓΙΚΗ ΕΤΑΙΡΕΙΑ

ΙΑΤΡΙΚΟΣ ΣΥΛΛΟΓΟΣ ΗΡΑΚΛΕΙΟΥ

Hot topics in Reproductive Medicine



SSRHR

INTERNATIONAL MEETING

Aquila Atlantis Hotel

Heraklion
Crete

November 03 05 2017

FINAL PROGRAMME & BOOK OF ABSTRACTS

ORGANIZER: SSRHR

Antonis Makrigiannakis MD, PhD
Professor of Ob/Gyn, University of Crete
Meeting Chairman

The meeting will be granted with 19 CME CREDITS by the Hellenic Medical Association

MEETING SECRETARIAT: ERA Ltd

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17, Asklipiou Str., 106 80 Athens-GREECE
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Scientific Society of Research in Human Reproduction

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Antonis Makrigiannakis MD, PhD

Professor of Ob/Gyn, University of Crete

Meeting Chairman

For more detailed instructions please visit the

www.ssrhrmeetings.com

Hot topics in Reproductive Medicine

INTERNATIONAL MEETING

Atlantis Hotel **Heraklion Crete**

November 03-05, 2017

SSRHR

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ORGANIZED BY

Scientific Society of Research in Human Reproduction

UNDER THE AUSPICES OF

UNIVERSITY OF CRETE SCHOOL OF MEDICINE

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Invitation

Dear Colleagues and Friends,

On behalf of the Organizing Committee, I have the pleasure to welcome you all to the **International Meeting of the Scientific Society of Research in Human Reproduction (SSRHR)** which will be held in Crete, Greece from **03** to the **05 November 2017,** at the **Aquila Atlantis Hotel in Heraklion, Crete.**

This year at the **SSRHR Meeting** we hope that we will provide the opportunity for professionals, practitioners and specialists alike from across the globe, to gather for meaningful discussions, exchange ideas and opinions and learning throughout plenary sessions, invited lectures, symposia and panel sessions.
The theme of the Meeting is **"Hot topics in Reproductive Medicine"** and its main topics, will be:

ANDROLOGY
ENDOMETRIOSIS
ENDOMETRIUM
FERTILITY PRESERVATION
HPV AND INFERTILITY
HYSTEROSCOPY
IMMUNOLOGY OF IMPLANTATION
IMPLANTATION
MENOPAUSE
ORAL CONTRACEPTIVES
OVARIAN STIMULATION
P.O.F
REPEATED IMPLANTATION FAILURE
REPRODUCTIVE ENDOCRINOLOGY
REPRODUCTIVE SURGERY IMAGING IN GYNECOLOGY
STEMM CELLS
ULTRASOUND IN GYNECOLOGY

The Meeting will have Oral Presentations and we invite all authors to submit abstracts related to the above topics.

We are looking forward to welcome you all and wishing and hoping to share with you this scientific and cultural experience.

Antonis Makrigiannakis MD, PhD
Professor of Ob/Gyn, University of Crete
Meeting Chairman

FREE ENTRANCE

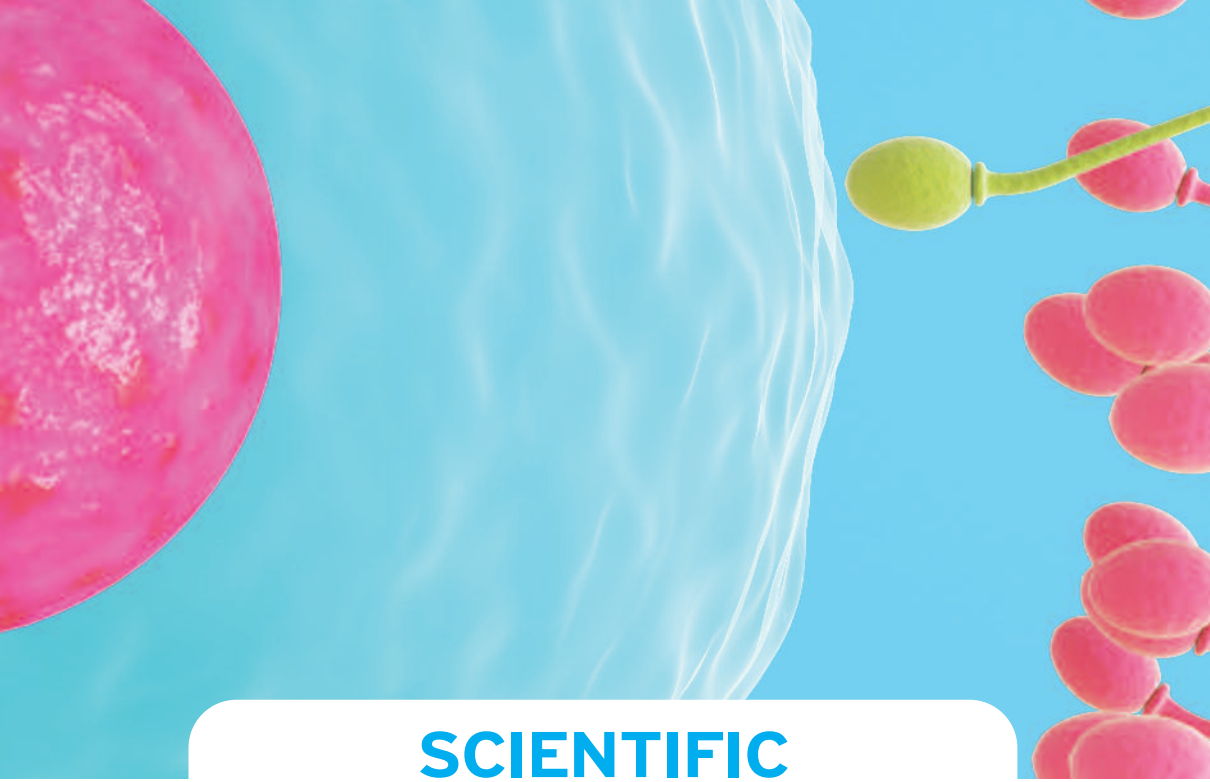
Vasiliki St. Marcus

FRIDAY 3 November 2017, 20.00p.m.

Women in the urban Heraklion of the 20th century

*Speech by **Starida Liana**, Archaeologist*

The event is coordinated by Mara Panagiotaki, historian



SCIENTIFIC
Program

Hot topics in Reproductive Medicine

INTERNATIONAL MEETING

Atlantis Hotel **Heraklion Crete**

November 03-05, 2017

SSRHR

13:45-14:45 Oral Presentations
Chairmen: **Ziogos E., Rasidaki M.**

O.P. 01 MANAGEMENT OF CORNUAL ECTOPIC PREGNANCY
Matalliotakis M., Velegrakis A., Onze V., Karypidis T., Niraki E. Matalliotakis I.
Department of Obstetrics and Gynecology, Venizeleio General Hospital, Greece

O.P. 02 EMBRYONIC AVB3 INTEGRIN EXPRESSION IN 2-CELL AND 4-CELL MOUSE EMBRYOS AFTER OVARIAN STIMULATION
Anifantaki A.[1], Fraidakis M.[1], Tsakoumi P.[1], Mathioudakis E.[1], Neofytou E.[2], Stathopoulou C.[3], Athanasaki E.[4]
[1]Crete Fertility Centre, Heraklion Crete, Greece
[2]Medical School- Aristotle University, Unit for Human Reproduction- 1st Dept of Obstetrics and Gynecology, Thessaloniki, Greece
[3]Institute of Molecular Biology and Biotechnology, Foundation for Research and Technology, Heraklion Crete, Greece
[4]Department of Biology, Laboratory of Immunology, University of Crete, Heraklion, Crete, Greece

O.P. 03 ENDOMETRIAL MICROBIOTA AND IMPLANTATION
Bachlitzanaki E., Bachlitzanakis E., Papadakis E., Makrigiannakis A.
Department of Ub/Gyn, University of Crete

O.P. 04 SECRETOMICS AND THEIR ROLE IN IMPLANTATION
Choutas V., Mikelopoulos I., Fragouli I., Papakalodouka S., Makrigiannakis A.
Department of Ub/Gyn, University of Crete

O.P. 05 MALIGNANT THYMOMA, A RARE ENTITY DURING PREGNANCY
Michopoulou V., Patramani S., Psycharaki S., Furlan M., Karamani A., Martavantzis N., Makrigiannakis A.
University Hospital of Heraklion, Crete

O.P. 06 SEVERE OVARIAN HYPERSTIMULATION SYNDROME WITH PLEURAL EFFUSION: A CASE REPORT
Kokolakis I., Psycharaki S., Mitaras V., Drakakis I., Koutroulakis D., Ziogos E., Manidakis G., Makrigiannakis A.
University Hospital of Heraklion, Crete

O.P. 07 CORRELATION BETWEEN ART, INFERTILITY AND BIRTH DEFECTS
Onze V., Velegrakis A., Matalliotakis M., Demosthenous E., Matalliotakis I.
Obstetrics and Gynecology department - Venizeleio General Hospital - Heraklion,Greece

O.P. 08 **POSTMENOPAUSAL UTERINE BLEEDING AND ENDOMETRIAL THICKNESS**
Stratoudakis G., Kontezakis P., Kriaras A., Kkese K., Ebrahim H., Daskalakis G.
Department of Obstetrics & Gynecology of General Hospital of Chania, Crete, Greece

15:00-16:30 **SESSION I: Gynecologic - Endocrinology I**
Chairmen: **Messinis I., Kalantaridou S.**

- Natural menstrual cycle. Feedback mechanisms
  Messinis I.
- Dysfunctional bleeding of puberty
  Dafopoulos K.
- Obesity and disturbances of the menstrual cycle
  Adonakis G.
- Polycystic ovary syndrome (PCOS)
  Kalantaridou S.

16:30-17:00 COFFEE BREAK

17:00-18:15 **SESSION II: Gynecologic - Endocrinology II**
Chairmen: **Messinis I., Limperis V.**

- Hormonal Contraception
  Drakakis P.
- Amenorrhea. Diagnosis and treatment
  Makrigiannakis A.
- Menopause and cancer risk
  Daponte A.

18:15-18:45 **KEY NOTE LECTURE**
Chairmen: **Makrigiannakis A., Veiga A.**

- From Egg to embryo. A peripatetic journey
  Ebner T.

20:00-21:00 **Opening Ceremony**
Vasiliki St. Marcus

- Women in the urban Heraklion of the 20th century
  Mrs Starida Liana, *Archaeologist / Writer*

07:45-09:00 **Oral Presentations**
Chairmen: **Adonakis G., Pontikaki A.**

O.P. 09 **GENETIC SCREENING IN ASSISTED REPRODUCTION: LEGAL AND ETHICAL ISSUES**
Milapidou M. AUTh, Bosdou J. AUTh, Kipouridou K. AUTh, Tsalidis A. AUTh, Vasileiou M. AUTh, Chortara T.
Laboratory for the research of medical law and bioethics AUTh

O.P. 10 **CLINICAL EXOME SEQUENCING SCREENING OF INFERTILE INDIVIDUALS PARTICIPATING IN A SURROGACY PROGRAM: A PILOT STUDY**
Daphnis D., Argyriou A.[1], Constantoulakis P.[2], Giakoumakis I.[1]
[1]Mediterranean fertility Institute, [2]Science Labs NIPT

O.P. 11 **OVARIAN FUNCTION OF CHILDHOOD CANCER SURVIVOR - ADOLESCENT GIRLS**
Hatzidakis VE.[1], Moschovi M.[2], Messaropoulos P.[1], Neofytou S.[1], Vrachnis N.[1], Salakos N.[1], Deligeoroglou E.[1], Makrigiannakis A.[3], Kalantaridou S.N.[1]
[1]Unit on Primary Ovarian Insufficiency, 2nd Department of Obstetrics & Gynecology, University of Athens School of Medicine, "Aretaieion" Hospital, Athens, Greece;
[2]Hematology-Oncology Unit, First Department of Pediatrics, University of Athens School of Medicine, Aghia Sophia Children's Hospital, Athens, Greece;
[3]Department of Obstetrics & Gynecology, University of Crete School of Medicine, Heraklion, Greece Hematology-Oncology Unit, First Department of Pediatrics, University of Athens, Aghia Sophia Children's Hospital, Athens, Greece
Hematology-Oncology Unit, First Department of Pediatrics, University of Athens, Aghia Sophia Children's Hospital, Athens, Greece

O.P. 12 **PARTIAL HYDATIDIFORM MOLE AND COEXISTING FETUS DURING SECOND TRIMESTER: A CASE REPORT**
Christoforaki V., Kokolakis I., Michopoulou V., Gkatzoudi K., Makrigiannakis F., Koutroulakis D., Pontikaki A., Rasidaki M., Makrigiannakis A.
University Hospital of Heraklion, Crete

O.P. 13 **SPLENIC PREGNANCY TREATED NON-OPERATIVELY WITH SELECTIVE EMBOLISM AND METHOTREXATE**
Drakakis I., Patramani S., Goudeli C., Mitaras V., Makrigiannakis F., Karamani A., Ziogos E., Makrigiannakis A.
University Hospital of Herakleion, Crete

O.P. 14 **THE EFFICACY OF INTRAUTERINE DEVICES FOR EMERGENCY CONTRACEPTION**

Stratoudakis G., Kontezakis P., Kriaras A., Kkese K., Ebrahim H., Daskalakis G.
Department of Obstetrics & Gynecology of General Hospital of Chania, Crete, Greece

09:00-10:15 **SESSION III: Embryology**

Chairmen: **Veiga A., Balaban B., Ebner T.**

- New biomarkers of objective embryo selection, do they improve the implantation potential?
  Balaban B.
- Blastocyst Stage Cryopreservation: Toward Single Embryo Transfer Policy
  Kovacic B.
- Treatment of mitochondrial disease by nuclear transfer.
  A role in Infertility?
  Veiga A.

Expert Panel: Metaxas E., Kanakas N., Dimitrakopoulos P.

10:15-11:30 **SESSION IV: Endometrium - Embryo Dialogue. How to achieve implantation Success**

Chairmen: **Messinis I., Motrenko T., Tarlatzis B.**

- Preimplantation genetic screening: A valid approach for repeated implantation failure
  Gianaroli L.
- Increasing Endometrial receptivity: the impact of uterine microbiome
  Jesche U.
- The impact of microbione in Reproduction
  Gurgan T.
- The role of immune modulating agents during implantation and pregnancy
  Makrigiannakis A.

Expert Panel: Tryfos D., Promponas E., Sirkos St.

11:30-12:00 COFFEE BREAK

SATURDAY 04 November

12:00-13:00 **FERRING SYMPOSIUM: Personalization of the ovarian stimulation: Challenging the myths, crafting the future**
Chairmen: **Makrigiannakis A., Dafopoulos K.**

- George Lainas (Athens): "The limits of the natural cycle concept"
  Lainas G.
- Individualization in practice: The evidence for follitropin delta
  Christophoridis N.
- The significance of the right oocyte yield
  Sfakianoudis K.

13:00-13:30 **MERCK LECTURE**
Chairmen: **Makrigiannakis A., Karatzis P.**

- Ovarian response and personalised efficacy
  Dafopoulos K.

13:30-14:00 **FERTILLAND LECTURE**
Chairmen: **Loutradis D., Giakoumakis I.**

Evidance Based management of poor ovarian response
Kolibianakis S.

Expert Panel: Kitseli M., Kondylis P., Peristeris I., Riga A.

14:00-15:00 LUNCH BREAK

15:00-16:30 **SESSION V: Diagnosis and treatment of PCOS**
Chairmen: **Gurgan T., Loutradis D.**

- What is the best protocol for ovarian stimulation in PCOS women undergoing IVF
  Tarlatzis B.
- Endocrine Status and Ultrasound Markers of PCOS
  Motrenko T.
- Updates in Ovulation Induction in patients with PCOS
  Tavmergen E.
- Fresh versus Frozen embryo transfer in PCOS patients?
  Tavmergen E.N.

Expert Panel: Sotirhos A., Kelaris V., Patrikios G.

SATURDAY 04 November

16:30-17:00 **FARAN S.A LECTURE**
Chairman: **Nikolettos N.**

- Mitocondrial dysfunction in human reproduction, the role of micronutrients
  Dattilo M.

Expert Panel: Stefanaki A., Bathrelos N., Kargakou M.

17:00-17:30 COFFEE BREAK

17:30-19:00 **SESSION VI: Controversial Issues**
Chairmen: **Watrelot A., Gurgan T., Vlachos N.**

- Epidemiology of tubal infertility and how to diagnose. HyCoSy still a need for endoscopy
  Adonakis G.
- Best option for ectopic pregnancy to operate or not? Management of interstitial pregnancy
  Vlachos N.
- Prognostic factors and evaluation scores for hydrosalpinges. When to operate?
  Watrelot A.
- Tubal Surgery in the era of ART
  Grimbizis G.

Expert Panel: Vagkou E., Vasilopoulos I., Megkoulas S.

21.00 FACULTY DINNER

07:45-09:00 Oral Presentations
Chairmen: **Vrekoussis T., Asmarianaki M.**

O.P. 15 AGE AT MENARCHE AND CLINICAL PREGNANCY OUTCOMES FOLLOWING ASSISTED REPRODUCTION TECHNOLOGIES
Vogiatzi P., Pouliakis E., Salamalekis G., Vrantza T., Alexiou E., Siristatidis C.
Assisted Reproduction Unit, 3rd Department of Obstetrics and Gynecology, Attikon Hospital, Medical School, National and Kapodistrian University of Athens, Athens, Greece

O.P. 16 IS CIGARETTE SMOKING AFFECT SEMEN PARAMETERS IN SUBFERTILE MEN SEEKING FERTILITY TREATMENTS: A COHORT STUDY
Salamalekis G., Vrantza T., Alexiou E., Siristatidis C.
Assisted Reproduction Unit, 3rd Department of Obstetrics and Gynecology, Attikon Hospital, Medical School, National and Kapodistrian University of Athens, Athens, Greece

O.P. 17 THE COMBINATION OF ENDOMETRIAL INJURY AND FREEZE ALL STRATEGY IN WOMEN WITH A HISTORY OF REPEATED IMPLANTATION FAILURE: A PILOT STUDY
Rigos I., Basios G., Salamalekis G., Vrantza T., Siristatidis C.
Assisted Reproduction Unit, 3rd Department of Obstetrics and Gynecology, Attikon Hospital, Medical School, National and Kapodistrian University of Athens, Athens, Greece-

O.P. 18 FRAGILE X PREMUTATIONS IN GREEK WOMEN WITH PRIMARY OVARIAN INSUFFICIENCY
Hatzidakis V.E.[1], Sofocleous C.[2], Messaropoulos P.[1], Neofytou S.[1], Salakos N.[1], Vrachnis N.[1], Deligeoroglou E.[1], Makrigiannakis A.[3], Kitsiou-Tzeli S.[2], Kalantaridou S.N.[1]
[1]Unit on Primary Ovarian Insufficiency, 2nd Department of Obstetrics & Gynecology, University of Athens School of Medicine, "Aretaieion" Hospital, Athens, Greece;
[2]Department of Medical Genetics, Choremio Research Centre, 1st Department of Pediatrics, University of Athens School of Medicine, Athens, Greece;
[3]Department of Obstetrics & Gynecology, University of Crete School of Medicine, Heraklion, Greece

O.P. 19 PLACENTA PRAEVIA-TWO YEARS EXPERIENCE OF OUR CENTER
Pontikaki A., Goudeli C., Christoforaki V., Kokolakis I., Gaitanis K., Furlan M., Rasidaki M., Makrigiannakis A.
University Hospital of Heraklion, Crete

O.P. 20 **THE ROLE OF ULTRASOUND IN THE POSTMENOPAUSAL CYSTIC ADNEXAL MASSES**

Stratoudakis G., Kontezakis P., Kriaras A., Kkese K., Ebrahim H., Daskalakis G.
Department of Obstetrics & Gynecology of General Hospital of Chania, Crete, Greece

09:00-10:15 **SESSION VII: What is new in ART?**
Chairmen: **Loutradis D., Messinis I.**

- Adenomyosis and endometriosis: impact on Art
  Sefrioui O.
- How can thrombophilia cause implantation failure or miscarriages
  Siristatidis S.
- New guidelines on Reccurent Miscarriages what we have to think about
  Toth B.

Expert Panel: Diamantis D., Polydorou A., Tzortzinis D.

10:15-10:45 **Angelini Pharma Hellas SA LECTURE**
Chairman: **Makrigiannakis A.**

Meriofert. How the placental origin of LH activity in the new hMG compound can offer possible advantages in Controlled Ovarian Stimulation
Ziegler D.

Expert Panel: Stefanis P., Karastefanou K., Karagiannidis L.

10:45-11:15 COFFEE BREAK

11:15-12:15 **KEY NOTE LECTURES**
Chairmen: **Papantoniou N., Drakakis P.**

- Novel aspects in the endocrinology of the menstrual cycle
  Messinis I.
- Genetic Predictors of ovulation induction regimes: where we are today?
  Loutradis D.

12:15-13:15 **SESSION VIII: Cancer and Fertility**
Chairmen: **De Bree E., Papantoniou N., Vardaki El.**

- Cervical screening from PAP test to HPV typing
  Vrekoussis T.
- Dynamic Reflectance Imaging and modeling of Cervix Enables the mapping of CIN related functional and microstructural Alteration
  Balas C.
- Treatment of cancerous cervical lesions. How do they affect the next pregnancy? A role in premature labor
  Sifakis S.

Expert Panel: Melistas V., Kosmas J.

13:15 **CLOSING REMARKS Makrigiannakis A.**

General Information

VENUE
The Meeting will be held in Heraklion, Crete at Aquila Atlantis Hotel.
2, Igias Street, Heraklion, 71 202 Crete, Greece
Tel: +30 2810 229 103 • Fax: +30 2810 226 265 • Web site: www.aquilahotels.com

DATES
The Meeting will be held on 03-05 November 2017.

LANGUAGE
ENGLISH is the official language of the Meeting.

TRADE EXHIBITION
An exhibition of scientific products, pharmaceuticals, instruments, equipment and relevant materials will be organized at the Meeting Venue.

REGISTRATION FEES
Those wishing to attend the Meeting should complete the enclosed registration form.

REGISTRATION (VAT INCLUDED)

General Participation	€ 246

The registration fees for participants cover:
• *Access to the scientific sessions and exhibition* • *Meeting material* • *Certificate of attendance*

ACCOMMODATION PACKAGE

For All Participants	€ 100

Rate includes: 1night accommodation bed & breakfast in single room, at the Aquila Atlantis Hotel

SCIENTIFIC PROGRAM
The Scientific program consists basically of State of the Art Presentations, Round Tables, Lectures, Case Studies, Oral and Poster Presentations.

CONTINUING MEDICAL EDUCATION
The meeting will be granted with 19 CME Credits by the Hellenic Medical Association.

SCIENTIFIC PRESENTATIONS
The Meeting Hall will be equipped with slide projectors for single or double projections 50 x 50 mm slides (24 x 36 mm transparencies), overhead projector, Screen, Data display projector for Power Point presentation, laser pointers etc.

SLIDE AND PC RECEPTION
A slide and PC reception desk for acceptance and checking of slides and PC disks will be located nearby the Meeting Hall. All slides and PC disks should be clearly labeled with the author's name and session's name. Speakers are kindly requested to hand out their slides or their PC disks at least 2 hours prior to their respective presentation.

CERTIFICATE OF ATTENDANCE
A certificate of attendance will be given to each registered participant, at the end of the Meeting.

SECRETARIAT AND HOSPITALITY DESK
The Meeting Secretariat desk will be located nearby the Meeting Hall and will operate throughout the Meeting hours.

CANCELLATION AND PAYMENT CONDITIONS FOR REGISTRATION AND ACCOMMODATION PACKAGE

CANCELLATION CONDITIONS

Cancellation requests must be made to the Meeting Secretariat in writing.

- For cancellation of registration, received by September 18th, 2017, a refund of the total fee, less 25% as administration charge, will be made. After that date refunds for registration will not be possible.
- For cancellation of accommodation package, received by September 25th, 2017, a refund of the total fee, less 50% will be made.
- From September 26th, 2017 refunds will not be possible.

PAYMENT CONDITIONS

- For registrations to be valid, full payment is required 50% of the accommodation package, payable to **ERA Ltd,** is required in order to confirm your Hotel Reservation
- Full payment for accommodation package should reach the Meeting Secretariat, not later than October 1st, 2017.

METHOD OF PAYMENT FOR REGISTRATION / ACCOMMODATION PACKAGE

Payment can be effected either:

a) By bank remittance stating the meeting's title, as well as the name of the participant:

- To Alpha Bank to the order of ERA Ltd Account No: **101.00.2002044307,**
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b) By major credit cards. Please complete the relevant information as described below.

Written confirmation will be sent by **ERA Ltd,** upon receiving your Reservation form.

WEB SITE

For the registration form and the most up-to-date information about the Meeting please visit the official website:

www.ssrhrmeetings.com

SECRETARIAT AND TRAVEL AGENCY

For all inquiries regarding: Meeting Activities and functions, Registration, Letter of invitation, Accommodation and Travel Reservations, Technical Services, Exhibition, Sponsoring, please contact:

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Acknowledgements

The Organizing Committee of the SSRHR International Meeting **"Hot topics in Reproductive Medicine"** expresses its gratitude to the below Companies that generously contributed to its materialization:

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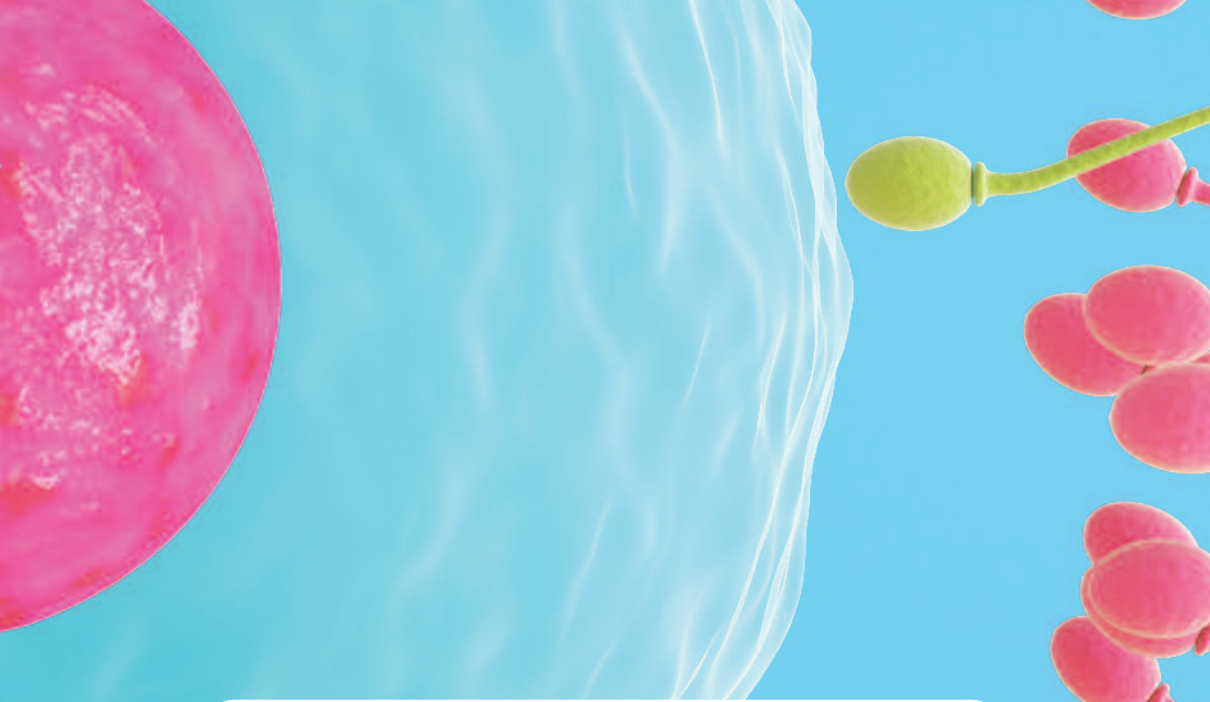

ORAL Presentations

Hot topics in Reproductive Medicine

INTERNATIONAL MEETING

Atlantis Hotel **Heraklion Crete**

November 03-05, 2017

SSRHR

O.P. 01

MANAGEMENT OF CORNUAL ECTOPIC PREGNANCY

Matalliotakis M., Velegrakis A., Onze V., Karypidis T., Niraki E., Matalliotakis I.
Department of Obstetrics and Gynecology, Venizeleio General Hospital, Greece

Background: Cornual pregnancy is an ectopic pregnancy that implants within the uterine horn. It makes up for 2-4% of all ectopic pregnancies. Maternal mortality is increased due to the elevated risk of uterine rupture and hemorrhagic shock.
Aim: To describe the management of a case.
Methods and Results: A 37 years old hemodynamically stable multiparous woman; presented with acute pelvic pain with minor vaginal bleeding and amenorrhea for 2 months. Medical history: Regular menstrual cycles, 2 CS. US: thin endometrium with a suspicion for a right adnexal mass. Admission day, β-HCG level: 2361.34 mIU/ml. Day 1, β-HCG level: 2770.42 mIU /ml. A single dose of Methotrexate was administered IM. Day 4, β-HCG level: 3086.06 mIU/ml. Day 7, β-HCG level: 2144.64 mIU/ml. Due to sudden right sided abdominal pain, vaginal bleeding and significant HCT drop, diagnostic laparoscopy was performed. Ruptured right cornual pregnancy was detected. Cornual resection was performed with the help of harmonic scalpel and diathermy.
Conclusions: In early pregnancy women may experience light vaginal bleeding and pelvic pain. Methotrexate, localized KCl injections and uterine artery embolization are offered when β-HCG levels are <5000 mIU/ml and in hemodynamically stable patients.
Laparotomy is required if massive internal hemorrhage occurs due to sudden uterine rupture. Laparoscopy offers cornual resection or cornuotomy. It is a minimally invasive and safe procedure and has the advantage of preservation of future fertility. However the obstetricians should be cautious since cornual resection may become the site of uterine rupture in a future pregnancy.
References
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O.P. 02

EMBRYONIC AVB3 INTEGRIN EXPRESSION IN 2-CELL AND 4-CELL MOUSE EMBRYOS AFTER OVARIAN STIMULATION

Anifantaki Aliki[1], Fraidakis Matthaios[1], Tsakoumi Paraskeui[1], Mathioudakis Emmanouil[1], Neofytou Eirini[2], Stathopoulou Chrysoula[3], Athanasaki Eirini[4]
[1]Crete Fertility Centre, Heraklion Crete, Greece
[2]Medical School- Aristotle University, Unit for Human Reproduction- 1st Dept of Obstetrics and Gynecology, Thessaloniki, Greece
[3]Institute of Molecular Biology and Biotechnology, Foundation for Research and Technology, Heraklion Crete, Greece
[4]Department of Biology, Laboratory of Immunology, University of Crete, Heraklion, Crete, Greece

Background: Integrins are glycoprotein-like heterodimeric molecules located on the surface of the cell, that act as receptors by regulating cellular interactions with extracellular matrix (ECM).The purpose of the present study was to investigate the effects of the ovarian stimulation protocol of mice on the expression of αvβ3 integrin in *in vivo* and *in vitro* conditions.
Method: Fertilized oocytes or embryos at the stage of 2 or 4 cells were isolated from the tubes of experimental mice in the presence or absence of ovarian stimulation. The embryos were either cultured for further growth and staining (*in vitro* conditions), or immunofluorescence stained for the αvβ3 or α5b1 integrin expression study (*in vivo* conditions).
Results: The results showed that the embryonic expression of integrinαvβ3 *in vitro* was more intense, though diffused, with respect to *in vivo* conditions in which staining was weaker but more organized. Ovarian stimulation, additionally, has shown to reduce the expression of α5b1 integrin in 2-cell embryos.
Conclusion: Embryonic expression of integrin αvβ3 in *in vivo* conditions was weaker but more organized and this is probably due to the natural conditions of interaction of the embryo with its environment, which is not present in embryos developed *in vitro*. Ovarian stimulation reduces the embryonic expression of αvβ3 integrin and this may have a negative effect on fetal development and implantation.

O.P. 03

ENDOMETRIAL MICROBIOTA AND IMPLANTATION

Matalliotakis Michail, Velegrakis Alexandros, Onze Vasileios, Karypidis Thomas, Niraki Eftychia, Matalliotakis Ioannis
Department of Ub/Gyn, University of Crete

Historically the uterus was assumed to be sterill.However, recent studies examine the existence of an endometrial microbiota, compare it with the nagiual one classify it as a lactobacillus dominated (>90% lactoacillus) or a non lactobacillus dominated rual result in implantation failure.
This findings consist a future tool for improving reproductive outcomes in infertile patients, underoing IVF.

O.P. 04

SECRETOMICS AND THEIR ROLE IN IMPLANTATION

Choutas V., Mikelopoulos I., Fragouli I., Papakalodouka S., Makrigiannakis A.
Department of Ub/Gyn, University of Crete

Secretomics are a promising tool to predict maternal-embryo implantation interface. Nowadays several studies highlighted secretomics as a step forward to assess endometrial functionality. The analysis of endometrial secretions located in the uterine fluid offers a window into human implantation, which was previously difficult to study non-invasively. Secretomics allow analysis during conception cycles due to their non-disruptive approach. Therefore secretomics may represent a valuable weapon in our arsenal not only to help us understand endometrial physiology but also to individually identify every woman's optimal time for implantation.

O.P. 05

MALIGNANT THYMOMA, A RARE ENTITY DURING PREGNANCY

Michopoulou V., Patramani S., Psycharaki S., Furlan M., Karamani A., Martavantzis N., Makrigiannakis A.
University Hospital of Heraklion, Crete

Aim: Thymoma is the most common tumour of the anterior mediastinum. Presentation during pregnancy is rare. Even rarer is the achievement of becoming pregnant after being diagnosed with thymoma. This is a report of a patient carrying out a pregnancy while on follow-up for thymoma B3 subtype-stage IVA.
Materials-Methods: A 22-year old woman was diagnosed with thymoma IVA after presenting with pain of the pleura and fever. The consulting thorasic surgeons decided that a radical surgery was not possible. She underwent 3 different series of chemotherapy resulting in stable disease. While on follow up she became pregnant. Termination was proposed and rejected. During her pregnancy, she required multiple aspirations of pleural effusion. A C-section was performed at 34th week due to fever and septic shock, and a healthy baby was delivered. Upon new scans, after she was discharged, significant disease progression was noticed. Decision for radiotherapy was made and followed through with success in reducing the mediastinal mass. The patient is now on follow-up with residual disease 7 years after its first diagnosis and 1.5 years after child birth.
Conclusion: Pregnancies after or during treatment for thymoma are very rare due to the high risk of recurrence. The rate of recurrence in a stage IVA thymoma is 35% in 5 years and 40% in ten years. It seems that when the above condition gets complicated with pregnancy those rates tend to increase but there is not enough literature to support it. There is a need for better understanding the change in natural history of slow and localized growth of thymoma to an accelerated one due to pregnancy.

O.P. 06

SEVERE OVARIAN HYPERSTIMULATION SYNDROME WITH PLEURAL EFFUSION: A CASE REPORT

Kokolakis I., Psycharaki S., Mitaras V., Drakakis I., Koutroulakis D., Ziogos E., Manidakis G., Makrigiannakis A.
University Hospital of Heraklion, Crete

Introduction: Ovarian hyperstimulation syndrome (OHSS) occurs when the ovaries are hyperstimulated and enlarged mainly due to fertility treatments, resulting in the shift of serum from the intravascular space to the third space. The severe form is characterized by hemo-concentration, thrombosis, pleural effusion, oliguria, rarely pericardial effusion, and respiratory distress. It can lead to life-threatening complications and even death. We report a case of severe ovarian hyper stimulation syndrome (OHSS) managed in our department.
Case presentation: A 30-year-old woman was referred to our hospital because of increasing abdominal girth, dyspnea and abdominal pain of 1 day's duration. The ultrasonographic examination revealed bilaterally enlarged multicystic ovaries and a large amount of ascites. She had an ovulation induction therapy and the embryo-transfer took place 9 days ago. The stimulation was performed by using a long protocol with follitropin alfa and hCG. The patient's weight was 81,8 kg, the height was 163 cm and the abdominal circumference 104,5 cm.

The patient showed a severe form of late-onset OHSS with massive ascites, abdominal pain, dyspnea, β-hCG 105.7 IU/L, hemoconcentration of 45.1%, hemoglobin of 14.9 g/dL and oxygen saturation of 95%. Immediately after admission, medical treatment was started. Body weight, abdominal circumference, intake and output, ultrasonography, and laboratory studies were performed daily. The patient reported increasing dyspnea. The chest X-ray revealed right pleural effusion Abdominal paracentesis for the drainage of the massive ascites was performed and a chest-tube was placed for treatment of pleural effusion. The patient was discharged to home after being hospitalized for 17 days.
Conclusion: Ovarian hyperstimulation syndrome (OHSS) is the most serious complication of controlled ovarian hyperstimulation. The late OHSS is more likely to be severe, due to endogenous reaction to hCG in an early pregnancy. The risk of OHSS can be reduced by monitoring gonadotropin therapy and by withholding human chorionic gonadotropin medication. OHSS must be treated urgently and with advanced management.

O.P. 07

CORRELATION BETWEEN ART, INFERTILITY AND BIRTH DEFECTS

Onze Vasileios, Velegrakis Alexandros, Matalliotakis Michail, Demosthenous Eythimios, Matalliotakis Ioannis
Obstetrics and Gynecology department - Venizeleio General Hospital Heraklion, Greece

Background: ART is divided into in Vitro Fertilization (IVF) and Intracytoplasmic sperm injection (ICSI). The method itself has been accused of an increased risk of congenital abnormalities (2.5%), compared to those derived from natural conception.
Aim: To review the published literature in order to investigate if there is any correlation between IVF *technique* and congenital birth defects.
Methods and results: A Medline databases search was conducted based on English language publications over a 40 year period. IVF, ICSI, congenital malformation, infertility and epigenetics represent the keys words used for this research.
Summary: Gastrointestinal, Urogenital, cardiovascular, musculoskeletal and Central Nervous System defects are the major types of congenital malformations observed in infertile couples. Studies have shown that the epigenetic changes assigned to the embryo at the early stages of fertilization and implantation in the ART process, occur mainly in the methylation of embryonic DNA.
These changes have been associated with various syndromes such as Beckwith-Wiedeman, Angelman Syndrome and Childhood neoplasias and an increased rate for subcutaneous fat deposition, lower body weight and higher blood pressure in the newborns. During the prenatal period, the embryo is influenced by several endogenous and exogenous factors that determine the growth and development.
It seems that infertility itself, male and female, is the main reason for the congenital malformations.
To conclude, ART has been associated with epigenetic changes in fetal DNA, which are associated with certain syndromes.
However, further investigation is required to determine the correlation between infertility and birth defects. Moreover, ART born infants should be followed up on a long term basis.
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O.P. 08

POSTMENOPAUSAL UTERINE BLEEDING AND ENDOMETRIAL THICKNESS

Stratoudakis G.,, Kontezakis P., Kriaras A., Kkese K., Ebrahim H., Daskalakis G.
Department of Obstetrics & Gynecology of General Hospital of Chania, Crete, Greece

Background: Postmenopausal bleeding (PMB) is a frequent event in postmenopausal women and represents up to 10% of all visits in gynecological practice. PMB is also highly suspicious of being a sign for the presence of endometrial cancer (EC) or premalignant lesions, as nearly every EC patient reports PMB at some point and around 5–12% of PMB results from EC.
Aim: To assess the diagnostic validity of transvaginal ultrasound (TVUS) measurements of endometrial thickness (ET) in patients with PMB for the detection of EC.
Methods: A retrospective analysis of data from patients presenting between January 2012 and June 2017 at our Department, with PMB and subsequent D/C was performed.
Results: The median patient's age at time of diagnosis was 64 years (ranging from 40 to 92 years). Thickness of the endometrium was significantly higher in women with EC than without, with a median ET of 14.3 mm for patients with EC and 9.0 mm for patients with no malignancy. Women with EC were older than women with no malignancy (median age 69 vs. 61 years). There were no differences between women with EC and women with no malignancy with regard to the hematological parameters. No associations between EC and the risk factors diabetes or hypertension or metabolic syndrome were found.
Conclusions: Older age and increased ET are significant and independent risk factors for the presence of EC in women with PMB. Thus, our data analysis supports the actual approach of histological evaluation of any PMB to confirm or exclude EC.
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O.P. 09

GENETIC SCREENING IN ASSISTED REPRODUCTION: LEGAL AND ETHICAL ISSUES

Milapidou Maria AUTh, Julia Bosdou AUTh, Kalliopi Kipouridou AUTh, Antonios Tsalidis AUTh, Marianna Vasileiou AUTh, Theodora Chortara
Laboratory for the research of medical law and bioethics AUTh

Background: The rapid progress of medical science now allows the extensive genetic screening of donors for a variety of diseases that may be transmitted to the child at a low actual cost. The question that arises is therefore to what extent the donor can be

tested. Some common bases have already been set on a European level (Directive 2006/17/EU and Articles 3 and 4 of Annex III of the Directive 2006/17/EC as amended by the Directive 2012/39/EU).
Aim: However, one should recommend the issuance of an appropriate and updated version of Directive at the European level, which will accurately determine the minimum and maximum content of medical checks the donor should undergo.
Methods: It is more than clear that an interdisciplinary approach (legal/medical) is needed to deal with this issues associated with the application of novel ART methods.
Results: The answers to the crucial questions posed, will form the basis of a Directive, that will be drafted, which will efficiently address most of the issues associated with implementation of ART methods.
Summary / Conclusions: The extensive genetic screening of donors for a variety of diseases is a controversial issue. So the adoption of a European Directive ruling this issue is of high priority.
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O.P. 10

CLINICAL EXOME SEQUENCING SCREENING OF INFERTILE INDIVIDUALS PARTICIPATING IN A SURROGACY PROGRAM: A PILOT STUDY

Daphnis Daphnis[1], Anastasios Argyriou[1], Pantelis Constantoulakis[2], Ioannis Giakoumakis[1]
[1]Mediterranean fertility Institute, [2]Science Labs NIPT

Recent advances in genome analysis using next generation sequencing (NGS) allows simultaneously analyzing hundreds and thousands of genes for mutations that either cause or predispose to diseases and/or pathologic phenotypes.
We have chosen to apply an advanced clinical exome sequencing panel (powered by Sophia Genetics DDM) on an Illumina NextSeq-500 platform that analyses in detail at least11 Mb of human expressed DNA that contain more than 4500 genes with disease-causing mutations, according to the Human Gene Mutation Database (HGMD).
We selected and targeted on 103 genes involved in human infertility, according to the Human Phenotype Ontology (HPO) database, which uses updated information from validated sources (Decipher, Orphanet, OMIM). The population we studied in this preliminary effort, were 10 patients that were participating in a surrogacy IVF program and exhibited unexplained infertility. Specifically, these patients have had at least two fresh embryo transfers in oocyte donation cycles with no positive result. Next generation sequencing and detailed bioinformatics analysis of the infertility related genes revealed pathogenic and/or likely pathogenic mutations in most of the infertile individuals.
The number of samples analyzed is very small to draw conclusive results, but this pilot study suggests that genetic factors that predispose to various fertility related functions may play significant role in cases of repeated IVF failures.
Given the significant cost and health burden of repeated efforts for each surrogacy program this new genomic era offers a novel approach in selecting the couples that must think of alternative reproduction options. In a surrogacy program such a test is significant since there are legal aspects that might prevent the couple from even entering the program if the test shows a pathogenic mutation.

O.P. 11

OVARIAN FUNCTION OF CHILDHOOD CANCER SURVIVOR -ADOLESCENT GIRLS

Hatzidakis VE.[1], Moschovi M.[2], Messaropoulos P.[1], Neofytou S.[1], Vrachnis N.[1], Salakos N.[1], Deligeoroglou E.[1], Makrigiannakis A.[3], Kalantaridou S.N.[1]
[1]Unit on Primary Ovarian Insufficiency, 2nd Department of Obstetrics & Gynecology, University of Athens School of Medicine, "Aretaieion" Hospital, Athens, Greece;
[2]Hematology-Oncology Unit, First Department of Pediatrics, University of Athens School of Medicine, Aghia Sophia Children's Hospital, Athens, Greece;
[3]Department of Obstetrics & Gynecology, University of Crete School of Medicine, Heraklion, Greece Hematology-Oncology Unit, First Department of Pediatrics, University of Athens, Aghia Sophia Children's Hospital, Athens, Greece

Background: Advances in childhood cancer treatment over the past decades have significantly improved survival, resulting in a rapidly growing group of survivors. However, both chemo- and radiotherapy may adversely affect reproductive function. Anti-Müllerian hormone (AMH) is an indicator of oocyte reserve in healthy females. The role of AMH testing in oncology remains investigational, although its sensitivity and stability over the menstrual cycle make it an attractive screening test for fertility assessment among female cancer survivors.
Aim: This is a preliminary study investigating menstrual characteristics and ovarian reserve in adolescent and early adulthood female childhood cancer survivors (CCSs).
Methods: The study population consists of 10 adolescent and young adult female survivors of childhood cancer treated in Greece (median age 17,5 years), at least 2 years after menarche.
Results: All participants have been treated with chemotherapy. Median AMH levels were 1,29 ng/mL (range 0,15 – 3,89), at a median time of 9,5 years (range 4 - 19) since cancer diagnosis and treatment. Although all patients reported normal menstrual cycles, 1/3 of the study population had very low AMH levels (below 1 ng/mL).
Conclusions: The present study will provide valuable information about the reproductive potential of survivors of childhood cancer. Female CCSs – even those reporting normal menstrual cycles – may have diminished ovarian reserve. Long-term follow up is need for this population

O.P. 12

PARTIAL HYDATIDIFORM MOLE AND COEXISTING FETUS DURING SECOND TRIMESTER:A CASE REPORT

Christoforaki V., Kokolakis I., Michopoulou V., Gkatzoudi K., Makrigiannakis F., Koutroulakis D., Pontikaki A., Rasidaki M., Makrigiannakis A.
University Hospital of Heraklion, Crete

Introduction: Hydatidiform mole is an abnormal pregnancy characterized by proliferation of cytotrophoblast and synciotrophoblast and vesicular swelling of placental villi. Partial hydatidiform mole and coexisting fetus is a rare condition that presents a dilemma for physicians and the parents of the fetus, particularly when it is detected during the second trimester of pregnancy.
Case presentation: A 31-year-old female (gravida2, para 0) was reffered to the OBGYN

department of University Hospital of Heraklion at 17 weeks and 2 days of gestation with suspected molar pregnancy. She presented with hyperemesis gravidarum, markedly increased β-HCG levels (>225.000iu/lt), hyperthyroidism and mild abdominal pain. At ultrasonography cystic placenta was identified, also the fetus was growth-restricted, presenting with a single umbilical artery and hyperechogenic bowel. Moreover, both ovaries were enlarged (7-9cm) and additional with mild abdominal distension appeared. She had a normal chest X-ray. So, increased β-HCG levels, as well as imaging studies and laboratory findings, indicated the presence of partial hydatidiform mole with no metastases. While she was inpatient, she also developed mild hypertension with positive urine spot. Termination of pregnancy by medical induction of birth was proposed. The couple disagreed and patient was discharged. One week later spontaneous abortion occurred and suction curettage was performed due to incomplete evacuation.
Conclusion: The management of partial mole pregnancies presents a dilemma for physicians and parents between expectant management and immediate intervention. A small number of cases where pregnancy was allowed to continue until 28 weeks of gestation or later have previously been reported resulting in a number of healthy babies. Parents must carefully be informed about the risk of potential maternal complications associated with molar pregnancy, including early-onset preeclampsia, hyperemesis gravidarum, persistent trophoblastic disease and metastases.

O.P. 13

SPLENIC PREGNANCY TREATED NON-OPERATIVELY WITH SELECTIVE EMBOLISM AND METHOTREXATE

Drakakis I., Patramani S., Goudeli C., Mitaras V., Makrigiannakis F., Karamani A., Ziogos E., Makrigiannakis A.
University Hospital of Herakleion, Crete

Introduction: Ectopic pregnancy occurs when the developing blastocyst becomes implanted at a site other than the endometrial lining of the uterine cavity. The spleen is one of the rarest sites for primary abdominal pregnancy. We report the first case of asymptomatic splenic pregnancy successfully treated non-operatively with selective embolization and adjuvant methotrexate administration intramuscularly.
Case report: A 30-year old female (g:3 p:2) was referred with a history of 10 weeks of amenorrhea, a diagnostic curettage which was histologically negative for chorionic villi, lack of ultrasonographic evidence of tubal pregnancy and ascending values of b HCG.
Upon admission, ultrasound showed no evidence of intrauterine or extrauterine pelvic pregnancy, b-HCG was 8150 mIU/l and PRG 3.3ng/ml. The patient was hemodynamically stable with no signs of haemoperitoneum. An abdominal ultrasound was performed and revealed evidence of a gestation sac at the superior aspect of the spleen without fetal pole or heart beat.
Following consultation with radiologists, embolization of the spleen targeting the gestation sac was decided, by selective catheterization of upper pole splenic artery branches.
Post embolization angiography revealed lack of vascularized tissue at the spleen's upper half.The patient tolerated the procedure well. Adjuvant treatment consisted of a single dose of methotrexate 50 mg/m2 (104mg) intramuscularly. On post-procedure day 1, bHCG levels dropped from 7750 to 2211 mIU/l. Recovery was uneventful with normalization of bHCG levels <20 mIU/l at day 20.
Conclusion: A high index of suspicion for abdominal ectopic pregnancy is required in order to diagnose the rare splenic gestation as early as possible prior to rupture and

avoid potential morbidity and mortality.In non-ruptured splenic gestations, non-operative treatment with selective embolization and complementary methotrexate intra-muscular injection can be considered as a promising therapeutic choice.

O.P. 14

THE EFFICACY OF INTRAUTERINE DEVICES FOR EMERGENCY CONTRACEPTION

Stratoudakis G., Kontezakis P., Kriaras A., Kkese K., Ebrahim H., Daskalakis G.
Department of Obstetrics & Gynecology of General Hospital of Chania, Crete, Greece

Background: Emergency contraception (EC) prevents pregnancy after unprotected sex or contraceptive failure EC may use drugs related to the female hormones estrogen and progesterone. These pills are similar to contraceptives pills but generally contain higher hormone doses. Another form of emergency contraception uses an intrauterine device
Aim: To compare one year intrauterine device (IUD) continuation among women presenting for emergency contraception and initiating the copper (Cu T380A) IUD or the levonorgestrel (LNG) 52 mg IUD.
Methods: We recruited women aged 19-40 years who reported unprotected intercourse in the previous 120 h and were interested in a same-day insertion IUD. The inclusion criteria also required a negative urine pregnancy test, desire to prevent pregnancy for at least 1 year, history of regular menstrual cycles (24–35 days) and knowledge of date of last menstrual period.
Results: Seventy-six women received IUDs; 40 (52.6%) chose the Cu T380A IUD and 36 (42.1%) chose the LNG 52 mg IUD. At 1 year, we accounted for 70 (92.1%) participants, 12 (17.2%) had requested removals, 6 (8.5%) had an expulsion and declined reinsertion, 2 (2.8%) had a pregnancy with their IUD in place and 50 (71.5%) were still using their device. The most common reason participants reported for IUD discontinuation in the first year of use was pain and/or bleeding. Conclusions: Two-thirds of women who chose IUD placement at the EC clinical encounter continued use at 1 year. Women initiating CuT380A IUD and LNG 52 mg IUD had similar one year continuation rates.
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O.P. 15

AGE AT MENARCHE AND CLINICAL PREGNANCY OUTCOMES FOLLOWING ASSISTED REPRODUCTION TECHNOLOGIES

Vogiatzi Paraskevi, Pouliakis Eythymios, Salamalekis Georgios, Vrantza Tereza, Eleni Alexiou, Siristatidis Charalampos
Assisted Reproduction Unit, 3rd Department of Obstetrics and Gynecology, Attikon Hospital, Medical School, National and Kapodistrian University of Athens, Athens, Greece

Background: A landmark event in female fertility is the menarche and by exploring the relevant time points compared to the clinical outcomes, a clearer distinction on

biological versus chronological ageing of the ovary and uterus could be achieved towards signifying reproductive potential.
Objective: To evaluate a possible relationship of age at menarche with clinical pregnancy in an IVF setting.
Methods: A retrospective analysis was performed on a study population of 391 women from July 2010 to February 2017 (mean age 35.1±3.6 years, min=24, max=40). The statistical analysis was performed by programming in SAS 9.3 for Windows, SPSS for Windows and Microsoft Excel.
Results: In the group when menarche occurred at <12 years, 18.18% of the women had clinical pregnancy in contrast to 26.20% in the group when menarche occurred at ≥12 years. The t-test proved that the age of menarche had statistically significant difference in the IVF outcome, as women with early menarche had smaller chance for clinical pregnancy ($p<0.05$). Logistic regression using the age of menarche (concordance level 49.0%), proved that the higher the age of menarche the higher the probability for successful clinical pregnancy with more than the half probability for clinical pregnancy.
Conclusion: Age at menarche appears to be statistically related to clinical pregnancy, as women <12 years at menarche had statistical lower percentage of achieving clinical pregnancy. The findings of this analysis suggest that age at menarche could be investigated as a surrogate parameter of reproductive potential in addition to medical history, clinical parameters and demographics.

O.P. 16

IS CIGARETTE SMOKING AFFECT SEMEN PARAMETERS IN SUBFERTILE MEN SEEKING FERTILITY TREATMENTS: A COHORT STUDY

Salamalekis Georgios, Vrantza Tereza, Alexiou Eleni, Siristatidis Charalampos
Assisted Reproduction Unit, 3rd Department of Obstetrics and Gynecology, Attikon Hospital, Medical School, National and Kapodistrian University of Athens, Athens, Greece

Background: Smoking status is well known to negatively affect the fecundity of women, but the role on semen quality still remains controversial.
Objective: To evaluate if cigarette smoking affects semen quality in a cohort of subfertile men.
Patients and Methods: In this retrospective cohort study, we included 317 consecutive men, partners of 317 subfertile couples seeking fertility counseling in our Unit. The study cohort was divided into two groups according to their habit to smoke more than 5 cigarettes up to 20 per day (group A, 73 men) and less than 5 cigarettes per day or never smoked (group B, 244 men) and associated eith with the results of the semen analysis according to the WHO 2010 criteria.
Results: In group A, 23% of the enrolled participants (37/73) had pathological semen parameters, while in 36 had a normal test. Of the 37 men with pathological sperm, 35% (13/37) had both low sperm concentration and low motility, 24% (9/37) had only low sperm concentration and 40% (15/37) had low motility with normal sperm concentration. In group B, 44% of them (107/244) had pathological semen parameters, while 121 had a normal semen analysis test and 16 were azoospermic. Of the 107 men with pathological sperm, 48% (52/107) had both low sperm concentration and low motility, 21% (23/107) had only low sperm concentration and 30% (32/107) had low motility with normal sperm concentration.
Conclusions: No significant statistical differences could be defined between cigarette smoking and sperm parameters in our retrospective cohort study of 317 subfertile men. Our study did not found any association between smoking and reduced semen quality.

O.P. 17

THE COMBINATION OF ENDOMETRIAL INJURY AND FREEZE ALL STRATEGY IN WOMEN WITH A HISTORY OF REPEATED IMPLANTATION FAILURE: A PILOT STUDY

Rigos Ioannis, Basios Georgios, Salamalekis Georgios, Vrantza Tereza, Siristatidis Charalampos
Assisted Reproduction Unit, 3rd Department of Obstetrics and Gynecology, Attikon Hospital, Medical School, National and Kapodistrian University of Athens, Athens, Greece

Background: Recent data suggest that the transfer of frozen embryo achieves equal or higher pregnancy rates. Therefore, the strategy of freezing all embryos and the transfer of frozen embryos in the next cycle is to be established as a standard practice. In addition, a promising method to increase the endometrial receptivity especially in women with repeated implantation failures is that of endometrial injury.
Aims: EW conducted a pilot prospective study to evaluate if endometrial injury performed after freeze all cycles and during the cycle before the frozen embryo transfer improves the pregnancy rates in women with failed implantations.
Methods: Fifteen patients were enrolled in this study. After a freeze all cycle, they were randomly allocated in two groups: an intervention group (n=7), who underwent endometrial injury before the transfer, and a control group (n=8), who underwent no other intervention. The primary outcome was clinical pregnancy rate, while secondary clinical and laboratory parameters. Baseline and cycle characteristics were also comparable between groups.
Results: There was a non-significant trend towards a higher clinical pregnancy rate in the intervention group [1/7 (14.3%) vs 0/8 (0%) p value with the fisher exact test 0.467]. Biochemical pregnancy rates were similar in the two groups [1/7 (14.3%) vs 1/8 (12.5%) p > 0.999].
Conclusions: Endometrial injury performed during the cycle before a frozen embryo transfer in women with RIF does not seem to improve clinical pregnancy rates, but definitely a randomized control trial with a larger sample size, would me more accurate.
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O.P. 18

FRAGILE X PREMUTATIONS IN GREEK WOMEN WITH PRIMARY OVARIAN INSUFFICIENCY

Hatzidakis V.E.[1], **Sofocleous C.**[2], **Messaropoulos P.**[1], **Neofytou S.**[1], **SalakosN.**[1], **Vrachnis N.**[1], **Deligeoroglou E.**[1], **Makrigiannakis A.**[3], **Kitsiou-Tzeli S.**[2], **Kalantaridou S.N.**[1]
[1]Unit on Primary Ovarian Insufficiency, 2nd Department of Obstetrics & Gynecology, University of Athens School of Medicine, "Aretaieion" Hospital, Athens, Greece;
[2]Department of Medical Genetics, Choremio Research Centre, 1st Department of Pediatrics, University of Athens School of Medicine, Athens, Greece
[3]Department of Obstetrics & Gynecology, University of Crete School of Medicine, Heraklion, Greece

Background: Fragile X syndrome (FRAXA) is a neurodevelopmental disorder that results from a single gene mutation on the long arm of the X chromosome. Carriers of Fragile X premutations were previously considered phenotypically normal, but are now known to be at risk for Primary Ovarian Insufficiency (POI). Approximately 20% of women with a permutation in the FMR1 gene have been reported to experience POI.
Aim: We are investigating the prevalence of Fragile X premutations in women attending our POI clinic who are willing to become pregnant without oocyte donation (i.e. only after spontaneous ovulation).
Methods: FMR1 cytosine-guanine-guanine repeat size was determined by PCR fragment analysis.
Results: Eleven women were referred for genetic analysis of the FMR1 gene. The median age was 32.5 years. Three out of 7 women (42.85%) were fragile X premutation carriers. Four FMR1 results are pending.
Conclusions: Women with POI may have spontaneous ovulation and become pregnant. The occurrence of fragile X premutation may lead to the birth of a boy with fragile X syndrome. Proper genetic analysis and counseling should take place before pregnancy occurs. Genetic counseling of family members is also an important issue for these patients.

O.P. 19

PLACENTA PRAEVIA-TWO YEARS EXPERIENCE OF OUR CENTER

Pontikaki A., Goudeli C., Christoforaki V., Kokolakis I., Gaitanis K., Furlan M., Rasidaki M., Makrigiannakis A.
University Hospital of Heraklion, Crete

Aim: Due to the increasing age of childbearing and the frequency of IVF and caesarian sections, the prevalence of placenta praevia, placenta accreta and vasa praevia is higher (5,2/1000 deliveries) with the highest rates in asian countries. Particularly, the frequency of placenta praevia has increased 13 times from the beginning of the 20th century. The advances of prenatal testing have increased the sensitivity of the prompt diagnosis of placental anomalies. Frequent consequences in pregnancies with placenta praevia are: second trimester hemorrhage (80%), preterm birth (>37 percentile), neonatal admission in the neonatal intensive care unit, higher percentage of perinatal and neonatal mortality, and small for gestational age fetuses (SGA).
Methods: During last year 33 cases of placenta praeviae attended in our clinic. The age of women in labour were 26-43 years old with mean age at 35 and gestational age from

25+1 until 38+4 weeks of gestation. 13 cases were primipara, 8 were second parity, 8 were third parity and 2 were fourth parity. The placental site was posterior in 16 cases, anterior in 6 cases and anteroposterior in 2 cases.
Results: The distribution of age in women with placenta praevia was similar above and under the age of 35.16/33 cases had a previous operation or caesarian section and 10 women conceived after IVF. 7/33 cases had placenta accreta and 5 of them had obstetric hysterectomy. The neonates were alive, able-bodied and cried immediately after delivery with Apgar score >7/10 1', >8/10 5'. 26 neonates were transferred to the neonatal intensive care unit.
Conclusion: The referral at a tertiary hospital for the optimal monitoring and treatment of the pathology of placenta is necessary. Over the recent years it has been proposed a conservative treatment with presurgical uterine artery embolization to reduce hemorrhage as well as the use of Methotrexate administration after surgery.

O.P. 20

THE ROLE OF ULTRASOUND IN THE POSTMENOPAUSAL CYSTIC ADNEXAL MASSES

Stratoudakis G., Kontezakis P., Kriaras A., Kkese K., Ebrahim H., Daskalakis G.
Department of Obstetrics & Gynecology of General Hospital of Chania, Crete, Greece

Background: Adnexal masses, which are located in the ovaries, the fallopian tubes, or any of the surrounding connective tissues, are pathologies commonly seen in the gynecology practice. The management of adnexal masses depends on their benign or malignant nature. Most of the ovarian cancers are epithelial in origin.
Aim: To evaluate the risk of malignancy in presumably benign adnexal masses in postmenopausal women.
Methods: 73 women with postmenopausal adnexal masses with a preliminary diagnosis of benign tumors were included. Age, duration of menopause, ultrasonographic findings (unilocular cysts, solid areas or papillary projections, and as multilocular cysts if they contained a septum or septa without any solid areas or papillary projections) and serum CA-125 levels were recorded preoperatively. The definitive diagnosis was based on postoperative histopathological examination.
Results: Of 73 adnexal mass, 6 (9.6%) were malignant, 66 (90.4%) were benign and one borderline (1.3%). There was no significant difference with regard to age and tumor size between the groups. A total of 18 women had bilateral lesions. Five of them were diagnosed with malignant tumors. There were also 12 multilocular cysts, three of them malignant. Out of 73 patients, 21 had solid areas, and 5 of them were diagnosed as malignant.
Conclusions: The presence of a solid component, bilateral lesions based on ultrasonography and high CA-125 values may be used as discriminative criteria, in the differential diagnosis of benign and malignant adnexal masses in postmenopausal women. No direct relation between the size of the adnexal mass and malignancy potential.
References:
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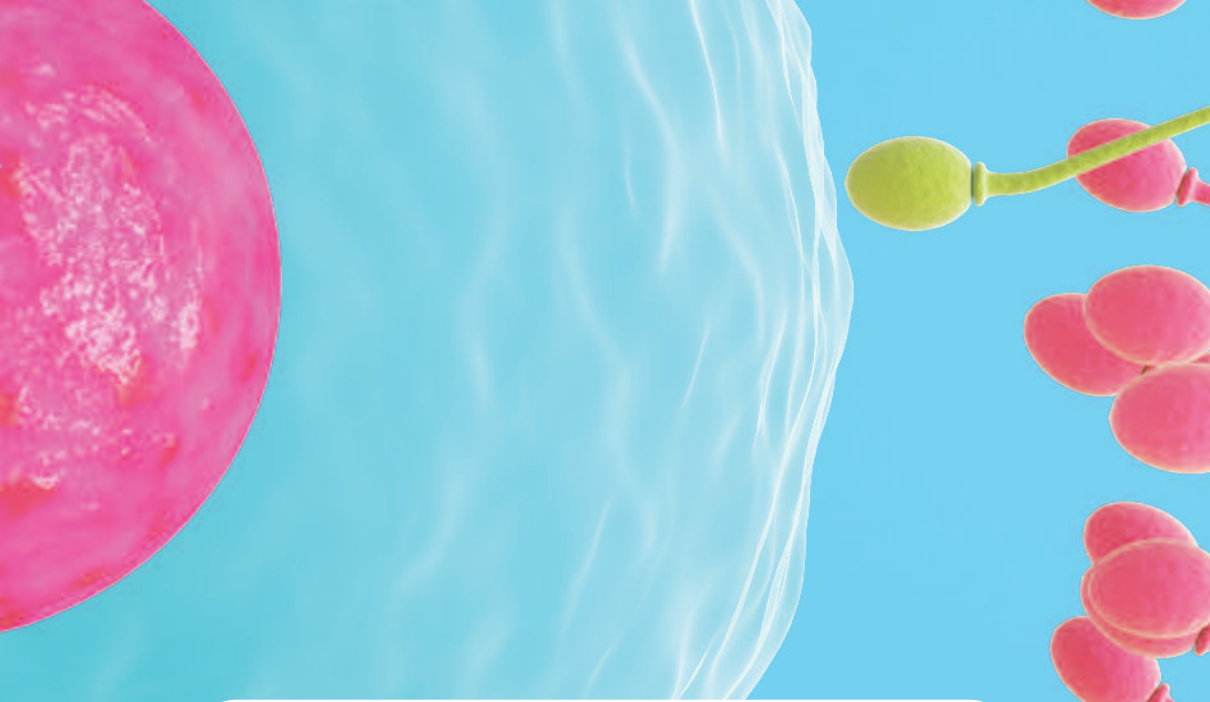

INVITED SPEAKERS' Abstracts

Hot topics in Reproductive Medicine

INTERNATIONAL MEETING

Atlantis Hotel **Heraklion Crete**

November 03-05, 2017

SSRHR

SESSION I GYNECOLOGIC - ENDOCRINOLOGY I

OBESITY AND DISTURBANCES OF THE MENSTRUAL CYCLE

George L. Adonakis MD
Assoc. Prof. of Obstetrics & Gynecology, University of Patras, Greece

Obese women often present with oligomenorrhea, amenorrhea or irregular periods. The association between obesity and heavy menstrual bleeding is not well documented and data on its prevalence are limited. While the investigation protocols should be the same as for women of normal weight, particular focus is required to rule out endometrial hyperplasia in obese women. The treatment modalities of menstrual disorders for obese women will be, in principle, similar to those of normal weight. However, therapeutic outcomes in terms of effectiveness and adverse outcomes need special consideration when dealing with women with a high body mass index (BMI). Different treatment strategies are reviewed paying particular attention to the effect of weight on their efficacy and the challenges of providing each treatment option. This presentation aims to review the current literature and give some guidance, which will influence clinical practice.

POLYCYSTIC OVARY SYNDROME

Sophia Kalantaridou
Professor of Obstetrics, Gynecology and Infertility, 2nd Department of Obstetrics & Gynecology, University of Athens School of Medicine, "Aretaieion" Hospital, Athens, Greece

Polycystic ovary syndrome (PCOS) is an endocrine-metabolic disorder, characterized by the presence of chronic oligo-ovulation or anovulation, hyperandrogenism and polycystic ovaries. The diagnosis is made in women with at least two of the following features: hyperandrogenism (clinical, biochemical, or both), ovulatory dysfunction and polycystic ovarian morphology. Nonclassic congenital adrenal hyperplasia, hyperprolactinemia and hypothyroidism should be ruled out. Women with PCOS are at increased risk for infertility, endometrial hyperplasia and cancer, obstructive sleep apnea, depression, insulin resistance and cardiovascular risk factors, such as dyslipidemia, hypertension, obesity and type 2 diabetes. Lifestyle modification is the first step for patients who are overweight or obese. Oral contraceptives are the first-line pharmacologic therapy, resulting in improvement of hirsutism, acne and menstrual pattern. Oral contraceptives also decrease the risk for endometrial hyperplasia and cancer. First-line treatment for infertility is clomiphene citrate; however, letrozole can also be used as first-line therapy. Gonadotropins and laparoscopic surgery can be used as second-line treatment. IVF is considered the third-line treatment, with the antagonist-based protocol being the preferred option, as it is associated with lower risk of developing ovarian hyperstimulation syndrome. Women with PCOS require long-term follow up; the early presence of cardiovascular risk factors underscores the need to screen and treat these women to prevent future cardiovascular disease, the leading cause of death in women.

MENOPAUSE AND CANCER

Alexandros I. Daponte, MD, FCOG
Professor, Head of the Department of Obstetrics and Gynaecology,
University of Thessaly, School of Health Sciences, Faculty of Medicine, Larissa, Greece

Risk of developing cancer increases as you enter menopause. Menopausal women have a greater chance of developing cancer because they're **older** and have an **increased body weight**. Although the association of adiposity with cancer risk has been extensively studied, associations for only 11 cancers (oesophageal adenocarcinoma, multiple myeloma, and cancers of the gastric cardia, colon, rectum, biliary tract system, pancreas, breast, endometrium, ovary, and kidney) were supported by recent strong evidence. Women in order to reduce their cancer risk during and after menopause should exercise, eat a healthy diet, don't smoke and maintain a healthy body weight. The importance of keeping a healthy body weight is emphasized by the fact that that gaining weight after menopause increases a woman's risk of breast cancer, but losing weight after menopause can actually reduce your risk.

Menopausal Hormone Therapy (MHT) and Cancer
Before the Women's Health Initiative (WHI) studies began, it was known that MHT with estrogen alone increased the risk of in women with an uterus. The most comprehensive evidence about risks and benefits of MHT comes from two. The **WHI Estrogen-plus-Progestin Study**, in which women with a uterus were randomly assigned to receive either a hormone medication containing both estrogen and progestin or a.
The **WHI Estrogen-Alone Study**, in which women without a uterus were randomly assigned to receive either a hormone medication containing estrogen alone or a placebo. More than 27,000 healthy women who were 50 to 79 years of age at the time of enrollment took part in the two trials. Although both trials were stopped early (in 2002 and 2004, respectively) when it was determined that both types of therapy were associated with specific health risks, longer-term follow-up of the participants continues to provide new information about the health effects of MHT. Research from the WHI studies has shown that MHT is associated with the following harms:
Breast cancer. Women who took estrogen plus progestin were more likely to be diagnosed with breast cancer. The breast cancers in these women were larger and more likely to have spread to the lymph nodes by the time they were diagnosed. The number of breast cancers in this group of women increased with the length of time that they took the hormones and decreased after they stopped taking the hormones. These studies also showed that both combination and estrogen-alone hormone use made less effective for the early detection of breast cancer. Women taking hormones had more repeat mammograms to check on abnormalities found in a screening mammogram and more breast biopsies to determine whether abnormalities detected in mammograms were cancer. The rate of death from breast cancer among those taking estrogen plus progestin was 2.6 per 10,000 women per year, compared with 1.3 per 10,000 women per year among those taking the placebo (9). The rate of death from any cause after a diagnosis of breast cancer was 5.3 per 10,000 women per year among women taking combined hormone therapy, compared with 3.4 per 10,000 women per year among those taking the placebo.

Lung cancer. Women who took combined hormone therapy had the same risk of lung cancer as women who took the placebo. However, among those who were diagnosed with lung cancer, women who took estrogen plus progestin were more likely to die of the disease than those who took the placebo. There were no differences in the number of cases or the number of deaths from lung cancer among women who took estrogen alone compared with those among women who took the placebo.
Colorectal cancer. In the initial study report, women taking combined hormone therapy had a lower risk of colorectal cancer than women who took the placebo. However, the colorectal tumors that arose in the combined hormone therapy group were more advanced at detection than those in the placebo group. There was no difference in either the risk of colorectal cancer or the stage of disease at diagnosis between women who took estrogen alone and those who took the placebo. However, a subsequent analysis of the WHI trials found no strong evidence that either estrogen alone or estrogen plus progestin had any effect on the risk of colorectal cancer, tumor stage at diagnosis, or death from colorectal cancer.
Women who had a and who are prescribed MHT generally take estrogen alone. In 2004, when the WHI Estrogen-Alone Study was stopped early, women taking estrogen alone had a 23 percent reduced risk of breast cancer compared with those who took the placebo. An analysis conducted after study participants had been followed for an average of 10.7 years found that women who had taken estrogen alone still had a lower risk of breast cancer than women who had taken the placebo, that continues for at least 5 years after they stop taking MHT. Women who take combined hormone therapy have an increased risk of breast cancer that continues after they stop taking the medication. In the WHI study, where women took the combined hormone therapy for an average of 5.6 years, this increased risk persisted after an average follow-up period of 11 years. Breast cancers diagnosed in this group of women were larger and more likely to have spread to the lymph nodes (a sign of more advanced disease).

KEY NOTE LECTURE

FROM EGG TO EMBRYO: A PERIPATETIC JOURNEY

Thomas Ebner
Prof.Dr., Kepler University, MedCampus IV, Krankenhausstr 26-30, A-4020 Linz, Austria

The ultimate goal of an IVF treatment is the birth of a healthy singleton. In order to minimize potential risks in ART (e.g., multiple pregnancy, ovarian hyperstimulation syndrome) both professional groups, clinicans as well as clinical embryologists, have to apply state-of-the-ART treatment. This does not only mean that controlled ovarian hyperstimulation, ovarian puncture and embryo transfer has to be performed according to evidence based medicine, but also, that all steps in the embryological laboratory have to be of high precision using modern technology. Sources of error are numerous and reach from suboptimal response to COH, failed pick-up, immaturity and bad quality of oocytes and embryos, failed fertilization and reduced blastulation. It is very likely that problems associated with the clinician s part cause a negative synergistic effect if lab procedures are performed suboptimal. It has to be clarified yet if natural cycle IVF or semi-managed cycles will increase outcome.

SESSION III EMBRYOLOGY

BLASTOCYST STAGE CRYOPRESERVATION: TOWARD SINGLE EMBRYO TRANSFER POLICY

Borut Kovacic
Department of Reproductive Medicine and Gynecologic Endocrinology, University Medical Centre Maribor, Slovenia

Assisted reproductive technology (ART) centers differ a lot from each other by embryo transfer and cryopreservation policies: by favourizing single or multiple embryo transfer, by developmental stages at which the embryos are transferred and at which they are cryopreserved, by morphological criteria of embryo suitability for transfer and for long-term storage and by cryopreservation methods used. The introduction of blastocyst culture in routine IVF allowed the reduction of the number of transferred embryos without significantly impairing the IVF treatment outcome. Many infertility specialists didn't trust in blastocyst culture in the beginning. One of the biggest concerns was related to the relatively unsuccessful blastocyst cryopreservation programme since blastocyst has been considered as a non-optimal stage for cryopreservation because of fluid filled blastocoel. With conventional slow freezing methods, it was not possible to dehydrate blastocysts enough during cryopreservation and survival and implantation rates after thawing were disappointingly low. The introduction of modified vitrfification method much more efficiently protected blastocysts against intracellular ice nucleation and consequently resulted in more than 90% survival rate. The pregnancy rate became comparable to that obtained with fresh blastocysts, which again increased the interest for blastocyst culture. Some prospective randomized studies comparing cumulative pregnancy rates from vitrified early embryos or blastocysts in freeze all patient group showed exactly the same outcomes in both groups. However, patients from blastocyst group concieved much earlier than patients with vitrified early embryos. Successful blastocyst vitrification programme encourages practitioners to advice patients elective single embryo transfer or even cancel transfers and vitrification of all available blastocysts in cases where severe ovarian hyperstimulation syndrome (OHSS) could appear. Author will present the experience from his country with governmental reimbursement programme for favourization elective single embryo transfer and experiences with »freeze all blastocysts« policy in patients having high risk for development of OHSS.

INCREASING ENDOMETRIAL RECEPTIVITY: THE IMPACT OF THE UTERINE MICROBIOME

Prof. Udo Jeschke
Department of Obstetrics and Gynecology, Ludwig-Maximilians-University Hospital, Maistrasse 11, 80337 Munich, Germany

Historically, the uterus and also the endometrium were assumed to be free of bacteria. Therefore, most of the already published data on the reproductive tract microbiome are based on vaginal samples.
Recent publication showed that the uterine cavity and the placenta are colonized with their own unique microbiome. These sides can be characterized as upper reproductive tract in comparison to the lower genital tract in the vagina.
Especially next generation sequencing (NGS) approaches and specifically analyses of the prokaryotic 16S ribosomal RNA genes (16S rRNA) revealed a number of new information on the upper genital tract microbiome and its influence on endometrial receptivity and pregnancy outcome.
16S metagenomics studies with the MiSeq System can achieve species-level identification of microbial populations efficiently. The workflow includes DNA isolation, library preparation, sequencing, and push-button analysis, delivering an end-to-end solution for 16S metagenomics. By combining the demonstrated Illumina library preparation protocol, the MiSeq System, and simple analysis software, researchers can analyze complex microbial samples quickly and easily.
The MiSeq system allows the analyses of 384 individual probes at one time (multiplex approach) at prices at around 50,-€/sample.
Based on that technology, recent publications could show that the microbiome of the lower genital tract is associated with preterm birth. Especially a *Lactobacillus iners* relative abundance in vaginal swabs is associated with increased risk of preterm birth. On the other hand, *Lactobacillus crispatus* dominance is highly predictive of term birth. With respective to the upper genital tract, data are not as prevalent as for the lower genital tract microbiome. Bacterial communities could be detected in the endometrial samples of all the subjects analyzed. *Lactobacillus* again was the most represented followed by *Gardnerella, Prevotella, Atopobium*, and *Sneathia*. In general, the bacteria community in the endometrium varied greatly from that in the vagina.
Analyses of the 20 most common bacteria strains in endometrial fluid samples from IVF patients with receptive endometrium showed that low abundance of endometrial *Lactobacillus* is associated with poor reproductive outcome. Therefore endometrial microbiota has an effect on implantation success or failure.
Bacterial colonization of the placenta is a common feature in normal and low-risk pregnancies. Bacteria may play a beneficial role for the fetus and the development of pregnancy. Preeclamptic placentas analyzed by 16S rRNA metagenomics, showed a bacterial composition normally associated with gastrointestinal tract infections (*Escherichia, Listeria, and Salmonella*), respiratory tract infections (*Anoxybacillus* and *K. pneumoniae*), and periodontal infections (*Dialister, Porphyromonas, Prevotella*, and *Variovorax*). Our own investigation showed that different parts of the placenta (cytotrophoblast and syncytiotrophoblast) reacted different towards infection with

Listeria monocytogenes (LM). We also tested the cytokine signature upon infection with *Listeria monocytogenes* (LM) in an *in vitro* model.
In conclusion, the uterine microbiome its impact on human reproduction is becoming better characterized. New methods like next generation sequencing (NGS) approaches and specifically analyses of the prokaryotic 16S ribosomal RNA genes (16S rRNA) will broaden our knowledge on that field. However, no consensus has been reached to date on whether an altered microbiome is responsible for a failed endometrial receptivity or the effect of it.

PREIMPLANTATION GENETIC SCREENING: A VALID APPROACH FOR REPEATED IMPLANTATION FAILURE

L. Gianaroli, A. Pomante, M.C. Magli
S.I.S.Me.R. Reproductive Medicine Unit – Bologna, Italy

Repeated implantation failure (RIF) can be defined as the failure of a couple to conceive after several transfers of good quality embryos.
Failure of implantation can be ascribed to maternal or embryonic causes. Maternal factors that negatively influence the implantation process are uterine malformations, thrombophilia, non receptive endometrium and immunological causes. The most common cause of implantation failure due to the embryo is related to chromosome aneuploidies. It has been reported that embryos from RIF patients show an higher incidence of aneuploidies than the embryos from control couples, and that in these embryos there is a major incidence of complex aneuploidies (involving 3 or more chromosomes).
RIF is also typical of patients carriers of structural rearrangements (translocations, inversions, deletions), since they produce a large number of aneuploid gametes and, as a consequence, of aneuploid embryos. Most of these embryos are unable to implant and even when this happen the pregnancy is destined to end up in a miscarriage.
Preimplantation genetic testing allows the identification of chromosomally normal embryos, with the aim to improve the outcome of IVF treatment, in terms of increased pregnancy rate, reduced time to pregnancy and decreased pregnancy loss.
Currently available techniques allow the simultaneous screening of all 24 chromosomes, with the possibility to identify also segmental aneuploidies or mosaic embryos.
The most commonly used methods for chromosome screening are array-CGH and Next Generation Sequencing. In the majority of cases, analysis is performed on trophectoderm cells, but there is a constant research for alternative sources of genetic material that could reliably represent the chromosomal status of the whole embryo and that can be easily obtained using less invasive biopsy method, such as blastocoelic fluid.
Aneuploidy, however, is not the only cause of implantation failure originating from the embryo. Other intrinsic factors can affect embryonic potential, impairing its ability to develop in utero and implant.
It has been demonstrated that mitochondrial DNA plays an important role in embryo development. The first approach on mtDNA analysis was its quantification in blastocysts, and the analysis of its correlation with implantation potential and pregnancy rate. Data from different studies revealed that embryos with a lower number of mtDNA copies have the best chances to generate a pregnancy and also that aneuploid embryos have a greater quantity of mtDNA.
The incidence of aneuploidies has also been related to some haplogroups that are more subject to develop chromosomally abnormalities, suggesting that, in addition to quantification studies, a more specific approach is needed.

ENDOCRINE STATUS AND ULTRASOUND MARKERS IN PCOS

Tatjana Motrenko Simic
Human Reproduction Centre, Budva, Montenegro

PCOS is complex endocrynopathy of normogonadotrophic normoestrogenic anovulation as a result of ovarian dysfunction, represented in 5-10% (by Rotterdam criteria up to 33%) of women reproductive age, and more in infertility group of patients. It is a heterogenic group of patients with clinical manifestation of menstrual irregularities, androgen excess signs, obesity, elevated serum LH, insulin resistance and metabolic syndrome. Diagnostic criteria for PCOS differ among societies, NIH/1999 simultaneously require both criteria - chronic anovulation and clinical and/or biochemical signs of hyperandrogenism (with exclusion of other aetiologies). Revised Rotterdam ESHRE/ASRM 2003 criteria mean 2 out of 3 criteria: oligo and/or anovulation, hyperandrogenism (clinical and/or biochemical signs), polycystic ovarian morphology (PCOM). Androgen Excess and PCOS Society/2009 requires the simultaneous presence of: hyperandrogenism (clinical and/or biochemical) and ovarian dysfunction (ovulatory dysfunction and/or polycystic ovarian morphology).
Endocrine status differ among PCOS since they are heterogenic group - lean, obese, younger, older, different expression of syndrome. Still in majority of cases elevated LH (60% day 3 in spontaneous cycles and after gonadotrophins)and LH:FSH ratio (40-50% od cases), hyperandrogenaemia (elevated testosterone, androstenedione, DHEA-S)around 50-60% cases, lower SHBG and consecutively higher FAI-free androgen index, hirsutism in one third of syndromes, increased fasting blood glucose and insulin resistance (less in lean cases).
Ultrasonography provides valuable information about ovarian morphology, following several parameters as well as relations with clinical manifestation: total ovarian volume, follicle number, ovarian stromal changes-echogenicity and area, ovarian stromal area/ total area ratio (S/A ratio), follicle distribution and blood flow – Doppler. The standard for imaging PCO is transvaginal high resolution 2D probe and scan should be performed in early follicular phase or in olygo-amenorrhoic patient's random, without previously used oral contraception or hormonal therapy. Polycystic ovarian morphology (PCOM) requires that even one ovary fit the criteria: more than 12 follicles between 2-9 mm on one ovary, or ovarian volume above 10 ccm, echogenic stroma. Mostly AFC and OV are used as parameter. Most of PCOS fulfil PCOM US criteria in 95% of cases.
Increased quality of ultrasound equipment – high resolution probes, 3-4 D, additional programs- provide more accurate view and allowed visualization of even smallest follicles resulting in increased incidence of PCO morphology in reproductive women population, especially younger, since AFC is age related. Comparing ultrasonography result in screening by PCOM for POCOS, it was suggested to reevaluate Rotterdam criteria of 12 follicles per ovary for more higher number – vary from 19 up to 25. In Lujan et all study, higher threshold was suggested after comparing sensitivity and sensibility of 12 and 26 value to distinguish healthy women from PCOS group, but only in case that sophisticated new ultrasonography equipment is used. Another study, Dewailly et all linked existing Rotterdam criteria to separate PCOS from controls. Then PCOM patients (FNPO >12) are separate from controls and all checked for AMH levels - AMH value of 28 pmol/l was threshold to identify women with mild and fully expressed PCOS from normal population.

Latest Report for Androgen Excess and PCOS Society (2014) suggest several conclusions: that we have to rise up threshold for PCOM in women 18-35 years of age if new ultrasound technology is used for AFC>25, maintained OV >10 ml, additional ultrasonography measurement like ovarian stroma and blood flow give no advantage, AMH and FNPO are similar diagnostic value, and just isolated PCOM not associate with other PCOS symptoms probably do not have health consequences, but for last conclusion additional studies still are needed.
What only PCO morphology mean? Underlying PCOS, or increased risk of hyperandrogenism, metabolic syndrome or Infertility problems? Since age related, how to interpret?
Age related -higher incidence was found in younger population by Rotterdam AFC criterion, in age group 18 – 22, PCOM is 69-84% (Rotterdam criteria based on studies with patients in late twenties, early thirties). Maybe it is more appropriate to adjust criteria to different age groups (*Duijkers IJ, Klipping C, 2010*).
Comparing US and age, TT, A, LH, AMH, ovarian volume and AFC in non-PCOS ovulatory women without HA, two homogenous clusters were found: I non PCOM non PCOS, and II PCOM, non PCOS. ROC Curve analysis was applied to distinguish non PCOM non PCOS from PCOS and the best compromise between sensitivity and specificity was: OV - at 7 ml, AFC – the best threshold value was 19 follicles (sensitivity 81 and 92%) and specificity (92 and 97%), for area under the curve 0,949 and 0,97,
AMH – threshold 35 pmol/L or 5 ng/ml. (Kristensen.S.*L. 2010*)
AFC decrease by time in both group - ovulatory and PCOS women (*Piltonen, 2005).* PCO morphology could become normal ovary - 50% of women with PCOM at mean age of 30 will have normal ovary in 8 year period (*Murphy MK. 2006).*
Most PCOS have PCO morphology. But PCOM do not necessary mean PCOS, just minority part of them is unrecognized PCOS. Non–hirsute eumenorrhoic patients with PCOM are functionally distinct but heterogeneous population. Majority - 53% have normal ovarian function (normal endocrine function), in 25% was occult PCOS (asymptomatic hyperandrogenemia, higher BMI, waist circumference, DHEA-S, lower SHBG) and 22% represent intermediate subgroup with17OHP hyperresponsiveness to GnRHag without hyperandrogenemia -younger, leaner, less PCOS biochemical abnormalities (*Mortensen M,2009*). PCOM in ovulatory women without hyperandogenism have no metabolic significance.
Adolescent population still remain with diagnostic challenges, starting from use of transabdominal sonography, normally high incidence of cycle irregularity, transitory hyperandrogenemia signs, insulin resistance and PCOM.
In conclusion, sonography is significant tool in diagnosis of PCOM and PCOS. PCOM prevalence is age dependent, but PCOM appearance is not prerequisite for diagnosis of PCOS, even is positively correlated with biochemical signs of PCOS. There is a need for additional tests in PCOM population like hormonal and metabolic tests since they are heterogeneous group of patients.

OVULATION INDUCTION IN PCOS

Prof. Erol TAVMERGEN
Scientific Director, Ege University Family Planning-Infertility Research & TreatmentCenter, Ege University Medical Faculty, Dept.of Ob&Gyn -Bornova-İZMİR-TURKEY
TAVMERGEN IVF CLINIC Scientific Director Izmir

Since its introduction 39 years ago, ART has become a commonly performed infertility treatment. ART is used to treat most cases of infertility, including male factor,

endometriosis, tubal disease, unexplained infertility and PCOS. PCOS, one of the most seen endocrinopathies in reproductive age women is seen in 3-10% of reproductive age women whereas it reaches almost 15% in infertile women. Due to its different types PCOS patients show different responses. Anovulation, hirstutism and PCOS are the clinical findings which lead to diagnosis. From the different studies performed those women with anovulation and hirsutism are the hardest group to achieve pregnancy.
PCOS has different mechanisms which influence infertility. As anovulation can be overcome by ovulation induction, the quality of the oocytes, embryos and endometrium are also influenced. One of the major problems in PCOS women are hyperresponse in ovulation induction.
The role of peroral used treatments such as aromatase inhibitors, metformin, inositol and also gonadotrophin treatments for non-IVF and IVF cycles, including GnRH Analogue triggering in Antagonist cycles as well total freezing strategies and Luteal Phase support will be discussed.

WHAT IS THE BEST PROTOCOL FOR OVARIAN STIMULATION IN PCOS WOMEN UNDERGOING IVF?

Professor Basil C. Tarlatzis, MD, PhD
Unit for Human Reproduction, 1st Dept. of Obstetrics and Gynaecology, Medical School, Aristotle University of Thessaloniki, Thessaloniki, Greece

In infertile women with PCOS wishing to conceive, IVF can be considered if the first and second line treatment options have failed or if there are other additional causes of infertility, such as tubal damage or male subfertility. The meta-analyses have shown that PCOS women undergoing IVF have a higher chance for cycle cancellation and a higher number of oocytes retrieved than the non-PCOS women, but there was no significant difference in clinical pregnancy, live birth and miscarriage rates. On the other hand, PCOS women have a significantly higher risk to develop moderate and severe OHSS.
The type of FSH used has no impact on the chances of pregnancy and OHSS, while the addition of metformin seems to decrease the risk for OHSS. The use of GnRH antagonists for suppressing premature luteinizing hormone (LH) surge is associated with a significant reduction in the incidence of OHSS as compared to GnRH agonists. In addition, it has made feasible the substitution of hCG with GnRH agonists and reliably eliminated the risk of clinically significant OHSS, due to the shorter duration of LH stimulation of corpora lutea as compared to hCG. This has changed dramatically clinical practise in ART, resulting in the virtual elimination of severe OHSS and the development of the "OHSS free clinic" concept, increasing in this way the safety of ovarian stimulation for ART to the benefit of infertile couples.
However, GnRH agonist triggering has been associated with a decreased chance of pregnancy, when embryo transfer is performed in the fresh cycle, probably due to the defective luteal phase from insufficient corpora lutea formation and function. To manage the problem of the decreased probability of pregnancy after GnRH agonist triggering in ovarian stimulation for IVF, it has been proposed to defer embryo transfer in a subsequent cycle. In this way, embryo transfer takes place in a normally developed endometrium with optimal chances to support implantation. The results from all available relevant studies, prospective and retrospective, in which GnRH agonist was used for triggering final oocyte maturation and no luteal phase support ("freeze all" strategy or donor patients), the incidence of severe OHSS was 0% (95% CI: 0 to 0). Moreover, the achievement of pregnancy in the frozen thawed cycles seemed to be very

satisfactory. In a very recent large RCT comparing fresh versus frozen embryo transfer after agonist triggering in PCOS women, it was shown that frozen embryo transfers were associated with significantly higher live birth rates as compared to fresh and significantly lower incidence of pregnancy loss and OHSS.
In conclusion, based on the available evidence, the preferred protocol for ovarian stimulation of PCOS women undergoing IVF is the use of GnRH antagonists to suppress premature LH surge, since it reduces the risk for OHSS and, in addition, allows to apply GnRH agonist triggering, which in combination with a freeze-all strategy, practically eliminates the occurrence of OHSS, while preserving very satisfactory live birth rates in the frozen thawed embryo transfer cycles.

FRESH OR FROZEN EMBRYO TRANSFER IN PCOS PATIENTS?

Prof. Dr. Ege Nazan TAVMERGEN GÖKER
Director, Ege University Family Planning and Infertility Research and Treatment Center
Ege University Department of OB&GYN, Bornova İZMİR, TURKEY

Implantation failures despite the new achievements in Assisted Reproductive Techniques, are being held responsible for most of the cycle failures.. Endometrial receptivity problems are the most common reasons for implantation failures. Endometrial receptivity is influenced by many factors such as ovulation induction methods, serum estradiol levels and endometrial pathologies as well as systemic problems. Slow freezing technologies have been the first choice techniques for many years, but due to the improvement of new technologies the vitrification method which is time consuming is introduced as a new technology of freezing in many centers. Embryo survival rates of over 95% has made vitrification a highly prefered method. These high survival and pregnancy rates have brought up a new treatment strategy as the ''FREEZE ALL'' technique.
Some centers have adapted this strategy to allmost all of their cycles. Still there are some clinical states where fresh embryo transfer isnot preferred. One of the most important status is the Ovarian Hyperstimulation Syndrome(OHSS) which in serious cases may end up in death.(3/100 000).PCOS patients are at special risk for OHSS. Early OHSS which cannot be prevented by only not transferring the embryos, can be prevented by using GnRH analogue trigger in GnRH Antagonist cycles. Although this type of triggering may diminish the risk of OHSS, it is well known that it negatively effects the receptivity of the endometrium and especially leads to lutealphase defects, thus lower implantation rates.
Since high progesterone levels at HCG trigger are also detrimental for implantation this may also be a reason to choose embryo freezing in PCOS patients.
Although the good pregnancy rates of freeze all cycles, there are also some doubts about using this strategy. The cryoprotectants that are being used and the procedure itself have given rise to some concerning questions. It is clear that these babies are heavier weight babies when compared to fresh transfer babies.These observations have lead to the questions if there is an epigenetic modification behind the increased weight babies. Preeclampsia is another issue that is being still debated on.The optimium priming protocoles are of great importance.
As a result, the delay in embryo transfer by using the cryopreservation method should be a good alternative in case of a need to get better pregnancy results. Still there are some doubts about the freeze all protocoles. More randomized study results are being needed to come to a conclusion as adapt to freeze all embryos.

EPIDEMIOLOGY OF TUBAL INFERTILITY AND HOW TO DIAGNOSE. HYCOSY STILL A NEED FOR ENDOSCOPY

George L. Adonakis MD
Assoc. Prof. of Obstetrics & Gynecology, University of Patras, Greece

Tubal factor infertility accounts for a large portion of female factor infertility. PID and Salpingitis seems to be the most common culprits causing tubal scarring and occlusion. The diagnosis of tubal occlusion can be established by a combination of clinical suspicion based on patient history and diagnostic tests, such as HSG, SHG, and laparoscopy with chromopertubation.

In case of suspected tubal infertility women who are not known to have co morbidities (PID, history of ectopic pregnancy or endometriosis) should be offered Hysterosalpingography as initial screening test; alternatively hysterosalpingography should be replaced with hysterosalpingo-contrast-ultrasonography if available and in case of associated comorbidities the patient should be subjected to laparoscopic chromopertubation.

Hysterosalpingography is the fluoroscopic visualization of the uterine cavity and fallopian tubes by injection of a radio-opaque contrast media and is credited with 84% sensitivity and 74.5% specificity. Tubal spasm is the culprit for lower accuracy of this diagnostic imaging technique but with the use of intravenous scopolamine and rotation of the patient it has been reduced to a minimum. HSG has two contraindications: PID and pregnancy (always perform the procedure during days 7-12 of the cycle), and a history of allergic conditions requires premedication with methylprednisolone 32mg for 12h and 2h in advance. Moreover HSG with an oil based contrast media has been proven to have a somewhat therapeutic role through flushing of tubal debris.

A hyperechogenic medium may enhance contrast visualization and enable clearer delineation of tubal anatomy. This may enhance confidence in the diagnosis of tubal patency, reduce false occlusion results, and improve the diagnostic yield of the test. Sonohysterography and hysterosalpingocontrast sonography are credited with 84.6% sensitivity and 99.7% specificity in detecting hydrosalpinx. Hysterosalpingo-contrast sonography evolved from using a negative contrast which is saline water to a positive contrast agent that is micro bubble agent and from 2D to 3D and even 4D imaging. HyCoSy is advantageous as patients exhibit a better pain tolerance, avoidance of iodinated contrast medium and preventing the use of ionizing radiation.

Laparoscopic chromopertubation remains the gold standard in evaluating the tubal infertility. Through the injection of diluted indigo carmine or methylene blue into the uterine cavity with simultaneous laparoscopy in order to visualize the tubal fill and spill into the abdomen. The disadvantages of this procedure are: expensive, invasive and requires anesthesia.

This presentation suggests a decision-making pathway based on the most current professional recommendations and available evidence. However, this presentation does not provide a definitive exposition of the methods used for investigating tubal patency. Rather, it explores the contexts in which the various investigations are most and least suitable, and identify their strengths and limitations.

PROGNOSTIC FACTORS AND EVALUATION SCORES FOR HYDROSALPINGES. WHEN TO OPERATE?

Antoine Watrelot
Hôpital NATECIA, Lyon-France

As early as 1999it was demonstrated by Strandell the deleterious effect of hydrosalpinges on IVF results. This study had be confirmed many times and therefore everybody agrees not to keep hydrosalpinx in patient refereed to IVF.
It is possible either to remove the tubes (salpingectomy) or to be conservative (salpingoneostomy)
We may consider today that conservative treatment may give similar results to those obtained in IVF in selected cases.
Selection of cases for conservative treatment depends on three criteriae: Tubal, technique and human.
1-The tubal factors allows to selection only tubes with good prognosis. Among the parameters, the quality of tubal mucosa is the most important. Various scores exist (for tubal mucosa, adhesions etc..) and allow to make a proper selection
2-technique: it has been demonstrated that this kind of surgery should be performed by experienced teams to obtain good success in term of pregnancy
3-Human: salpingectomy especially when bilateral is not well accepted and information and discussion with the patient are of paramount importance before deciding what option will be choosen.
If these criteriae are met, then conservative surgery is an attractive alternative allowing for the patient to conceive spontaneously and to have several pregnancy if wished.

ADENOMYOSIS AND ENDOMETRIOSIS: IMPACT ON ART

Omar Sefrioui
Gynécologue Obstétricien, General manager Anfa Fertility Center (Iso 9001-2008)
President de la Société Marocaine de Médecine de la Reproduction (SMMR)

Adenomyosis as endometrial disorder represents basal endometrial glands and stroma in the myometrium with reactive hyperplasia of the surrounding smooth muscle myometrial cells. Indeed, it is associated with enlarged uterus, pelvic pain, excessive vaginal bleeding while its effect on fertility and assisted reproductive technologies (ART) outcomes remains debatable. In the other hand, endometriosis is another challenge for treatment of infertility in women who desire to conceive. Endometriosis and adenomyosis are both diseases of Archimetra in uterus, suggesting that they are more consecutive tissular traumatization inducing chaotic reparation and proliferation of constitutive elements on Archimetra region with deep infiltration in uterus involving unbalanced immune profile. However, adenomyosis is affecting endometrial receptivity while endometriosis is in correlation with low number of oocytes retrieved and poor embryo quality. Indeed, with an affected junctional zone, they are causing endometrial receptivity disruption under unbalanced ovarian control and abnormal expression of P450 aromatase. However, medical treatment with aromatase inhibitor and GnRH agonist depot for at least 3 months prior to IVF appears to improve IVF outcomes. Moreover, frozen strategy following GnRH agonist pre-treatment, improves live birth rate.

Key Words: Adenomyosis, Endometriosis, oocyte, endometrium receptivity, IVF outcomes.

HOW CAN THROMBOPHILIA CAUSE IMPLANTATION FAILURE OR MISCARRIAGES

Charalampos Siristatidis, MD, PhD
Assisted Reproduction Unit, Third Department of Obstetrics and Gynecology, "Attikon Hospital", Medical School, National and Kapodistrian University of Athens, Rimini 1, Chaidari, Athens, Greece

The term "thrombophilia" is referred to conditions linked with increased risk of thrombosis. Both implantation failure and recurrent miscarriages are probably due to microvascular occlusion at the level of decidua. Whether congenital or acquired thrombophilia lead to both pathological conditions remains elusive.

Congenital thrombophilia is defined as a genetic predisposition to venous thromboembolism (VTE), through the alteration of a functional protein in the coagulation cascade. The predominant thrombophilic mutations include FVL mutation, prothrombin gene mutation G20210A, MTHFR mutation causing homocysteinaemia, and deficiencies of proteins C and S, and antithrombin. The relative risk of VTE is increased ×80 in women with a homozygous FVL or P2 gene mutation, whereas the risk is increased ×2.7 and ×3.8 in heterozygotes, respectively. Combined with the hypercoagulable state of pregnancy per se, thrombophilia has the potential to induce placental thrombosis and cause placental insufficiency from the early stages of conception. A second potential

mechanism is thrombosis of maternal vessels, which could reduce perfusion of the intervillous space leading to placentation failure causing early placental insufficiency. Damage of decidual or chorionic vessels, and/or reduction of trophoblast invasiveness, could lead to both conditions.
Also, some acquired conditions increase the risk of thrombosis. These include APS, heparin-induced thrombocytopenia, paroxysmal nocturnal hemoglobinuria, myeloproliferative disorders, particularly polycythemia vera and essential thrombocytosis, paraneoplastic syndrome, pregnancy, and increased estrogen levels. APS remains as a chronic thrombophilia, but "activated" during ART. Because of increased serum estradiol levels during ovarian stimulation and the luteal phase, may lead to vascular occlusion, while early pregnancy loss may occur through complement activation and inflammatory response, along with the disruption of oocyte development or uterine decidualization. The diagnostic criteria for this condition are strict and patients must be found to have antiphospholipid antibodies (anticardiolipin antibodies (aCL), and/or lupus anticoagulant (LA); and/or anti-β-2-glycoprotein I antibodies (aβ2-GPI)), persisting for two or more separate occasions, at least 12 weeks apart.
A major negative contribution theory is that of the hypothesis the endothelial dysfunction, one of the earliest manifestations of thrombotic phenomena, through the rise of the Th1 (i.e. interferon-γ, tumor necrosis factor-α) / Th2 cytokines (i.e. interleukin-10) ratio.
There are several arguments against the current hypotheses, especially that of placental vascular thrombosis, accompanied with the low quality of the studies that led to these conclusions. Interestingly, most meta analyses were constructed through case control and retrospective cohort studies with major methodological flaws and small sample sizes.

Further reading

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New guidelines on Reccurent Miscarriages what we have to think about

During her lifetime, almost every woman suffers from unrecognized miscarriage or failed implantation. Beside these spontaneous miscarriages, recurrent miscarriage (RM) can occur and is defined as three or more consecutive miscarriages <20 gestational weeks (WHO) or at least 2 consecutive miscarriages (ASRM). Recurrent miscarriage affects around 2-5% of women during their childbearing years. Primary RM refers to women without having a child, secondary RM to women with RM after a live birth. There are several established risk factors for RM including chromosomal, anatomical, endocrine, microbiological, psychological, hemostatic and immunological disorders.

Chromosomal disorders

Fetal chromosomal disorders are among the most relevant causes for spontaneous miscarriages. However, in 4-5% of the couples suffering of RM, chromosomal disorders are present, including translocations, inversions, mosaicism.
The guideline of the Royal college of Obstetrics and Gynecology (RCOG) recommends karyotyping of the abortive tissue, not the parents, whereas the guideline of the German, Suisse and Austrian Society of Obstetrics and Gynecology (DGGG, SGGG, OEGGG)

recommends karyotyping of the affected couple and/or the abortive tissue.
There are no curative therapeutic options in case of parental chromosomal disorders. However, patients can decide to undergo preimplantation genetic screening (PGS) or diagnostic (PGD). So far, there are no data supporting PGS in couples with RM as the live birth rates are equal to women conceiving spontaneously and the time to pregnancy seems to be shorter during natural cycle without PGS. Nevertheless couples with known severe chromosomal disorders benefit from PGD.

Hemostatic disorders
Several studies report possible associations between failed pregnancies and hereditary thrombophilia like mutations in the Faktor V Leiden (FVL; c.1601G>A in F5, rs6025) or Prothrombin G20210A gene (PT; c.*97G>A in F2, rs1799963), Antithrombin-, Protein C-, Protein S-, Protein Z- or Faktor XII-deficiency as well as elevated Faktor VIII or Lipoprotein (a). In addition there is data showing that polymorphisms in the Methylen-Tetrahydrofolatreduktase (MTHFR C677T bzw. c.665C>T), Angiotensin-Converting Enzyme (ACE) or Plasminogen-Activator-Inhibitor (PAI) gene are more common in women with RM. It has to be taken into consideration, that these hereditary thrombophilia are also common in general population indicating that it might be no monocausal risk factor for RM.
Most recently published international guidelines do not recommend standardized screening for hereditary thrombophilia in RM patients.
Low molecular heparin, which was offered for RM patients for many years in order to improve live birth rate, is no longer recommended to prevent RM, but can be applied to prevent maternal thrombosis during pregnancy.
Immunologic disorders
Although recent studies indicate that a subgroup of RM patients might suffer from immunologic disorders including elevated peripheral or uterine natural killer cells (pNK and uNK), alterations of the Th1/Th2 ratio, T4/T8 index and others, international guidelines recommend screening only for Anti-Phospholipid Syndrom (APLS) as an established immunologic risk factor in patients with RM. If RM patients fullfill the clinical and laboratory criteria of APLS (figure 1) Aspirin as well as low molecular weight heparin should be given, starting with positive pregnancy test.

Figure 1: APLS: clinical and laboratory criteria
Clinical criteria
≥1 venous or arterial thrombosis
1 or 2 unexplained miscarriages with morphologically normal fetus >10 gestational weeks
≥ 3 miscarriages < 10. gestational weeks
≥ 1 late miscarriage or premature birth < 34. Gestational weeks due to placental insufficiency or preeclampsia
Laboratory criteria (elevated levels must be proven 12 weeks after first diagnosis)
Anti-Cardiolipin - Ak (IgM, IgG) median to high levels
Anti-ß2-Glykoprotein-1 – Ak (IgM, IgG) high levels
Lupus Antikoagulant

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ANGELINI PHARMA HELLAS SA LECTURE

MERIOFERT®. HOW THE PLACENTAL ORIGIN OF LH ACTIVITY IN THE NEW HMG COMPOUND CAN OFFER POSSIBLE ADVANTAGES IN CONTROLLED OVARIAN STIMULATION

D. de Ziegler, MD
Dept of Obstetrics and Gynecology, Foch Medical Center – Universite Paris Ouest, Suresnes France

Controlled ovarian stimulation (COS) was developed for increasing the yield of ART by allowing the harvest of multiple oocytes and thus, the development of multiple embryos. COS was conceived in the hey days of ART for enhancing the efficacy of a procedure that bore little successes when performed in the menstrual cycle. The concept of COS therefore is to induce multiple follicular development by opposing the natural mechanism that control the ovulatory quota to one in humans. This is achieved by opposing the mid-follicular phase decrease in FSH, which is responsible for sending the smaller follicles of the cohort to atresia while allowing the larger follicle to mature. Historically, the decrease in FSH has been antagonized by either stimulating endogenous FSH production – using clomiphene citrate or aromatase inhibitors – or administrating exogenous FSH. The latter has been the most common mode of inducing COS in ART.
In the menstrual cycle, follicular recruitment in induced by a FSH elevation during the inter-cycle interval, which classically peaks approximately on cycle day 3. Further follicular development is pursued under LH dominance, when FSH declines under the influence of rising levels of E2. In COS, the role of LH – and LH dominance – in the late follicular phase was classically ignored. As soon as separation techniques and recombinant approaches allowed to develop pure FSH preparations, FSH-only approaches were recommended for COS.
More recently, ultra-pure gonadotropin preparations that foster FSH and LH effect properties have been developed and proposed in COS. RCT showed more favorable hormonal profile in COS conducted by hMG that combines FSH and LH effects as compared to protocols using recombinant FSH (recFSH). Notably, hMG protocols were associated with lower progesterone levels in end-follicular phase stages, as compared to findings made in women receiving recFSH.
Preparation providing FSH and LH effects are of different types. First a preparation exists that combines recFSH and LH recombinant origin (recLH). This however suffers from

the short half-life of recLH, which would warrant bi-quotidian administration for the desired efficacy on the end-follicular phase follicle. Second, another group of preparations – human menopausal gonadotrophines (hMG) – provides LH effects in addition to the FSH properties gained from hCG contained in the preparation. hMGs offer the advantage over recFSH/recLH preparations to provided sustained LH effects, as notably expressed by a more favorable end-follicular phase hormonal profile.

A phase III randomized controlled trial (RCT) compared the new ultra-pure hMG preparation, Meriofert®, to an older preparation (Lockwood et al. RBM on line 2017). While Meriofert gains its LH activity from added hCG of chorionic origin, the older preparation had hCG of pituitary origin. The difference in half-life of hCG of pituitary and chorionic origin – longer in the latter case – was responsible for different efficacy of the two products. The hMG preparation Meriofert resulted in more oocyte being retrieved despite similar hMG doses defined by the study protocol. Moreover, Meriofert resulted in a higher oocyte utilization rate with a higher mature-to-total-oocyte rate. Ultimately, there was a trend toward higher cumulative pregnancy rate in the Meriofert group.

In conclusion, recent data showed that hMG results in a more functional hormonal profile in the late phase of COS notably, with lower progesterone levels. The recent development of a hMG preparation gaining its LH effect from hCG of chorionic origin offers added efficacy, as compared to preparations using hCG of pituitary origin.

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