

Under the auspices of



UNIVERSITY OF CRETE
SCHOOL OF MEDICINE



ΙΑΤΡΙΚΟΣ
ΣΥΛΛΟΓΟΣ
ΗΡΑΚΛΕΙΟΥ



ΕΛΛΗΝΙΚΗ
ΜΑΙΕΥΤΙΚΗ &
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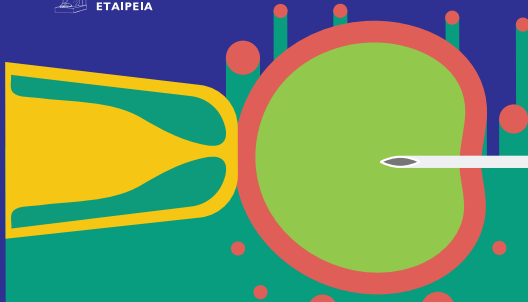


www.msrm.com



Scientific Society
of Research in
Human Reproduction

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19-21
OCTOBER 2018

MSRM

XV Annual Meeting

of the **M**editerranean **S**ociety for **R**eproductive **M**edicine

The meeting has been awarded
21 CME CREDITS by the Hellenic
Medical Association

**CRETE
GREECE**

IBIS STYLES HERAKLION
CENTRAL Hotel

HERAKLION

Final Program & Book of Abstracts

ΚΑΘΕ ΒΗΜΑ, ΚΑΘΕ ΛΕΠΤΟΜΕΡΕΙΑ ΣΤΗΝ IVF ΕΝΑΡΜΟΝΙΖΕΤΑΙ ΓΙΑ ΤΗ ΖΩΗ



Μετά απο 60 χρόνια συνεχιζόμενης καινοτομίας, γνωρίζουμε οτι σε έναν κύκλο IVF, η κάθε λεπτομέρεια έχει σημασία. Τα βήματα από την πρώτη ημέρα θεραπείας με γοναδοτροπίνες μέχρι την τελευταία, πρέπει να είναι τέλεια εναρμονισμένα, ώστε να δώσετε στη γυναίκα σιγουριά και τη μεγαλύτερη πιθανότητα για επιτυχή εγκυμοσύνη. Γι' αυτό η Merck είναι η μοναδική εταιρία που παράγει ένα σύνολο σκευασμάτων για όλο τον κύκλο IVF, ώστε να βοηθήσει να συντονίσετε κάθε βήμα της εξατομικευμένης θεραπείας. Διότι γνωρίζουμε οτι οι οικογένειες χτίζονται πάνω σε πολλές λεπτομέρειες που κάνουν τη διαφορά.

Λεωφόρος Κηφισίας 41-45 (Κτίριο Β), 151 23 Μαρούσι, Αθήνα, www.merck.gr

Με αφοσίωση στις λεπτομέρειες που κάνουν τη διαφορά

GONAL-f
COLLITROPINUS
Follitropin Alfa
Purified Fov

Pergoveris
(folliotropin alfa and lutropin alfa for injection)

Cetrotide
CETROTOLIN

VITRELLE
CHORIOGNADOTROPIN ALFA

Crinone
επίστυλιση 8%
8%

Luveris
LUTROPIN ALFA

MERCK

2 COMMITTEES - FACULTY

3 PRESIDENTS' MESSAGE

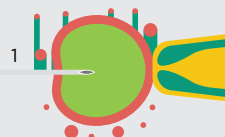
4-17 SCIENTIFIC PROGRAM

18-19 GENERAL INFORMATION

20 ACKNOWLEDGMENTS

22-36 ORAL PRESENTATION ABSTRACTS

37-62 INVITED SPEAKERS' ABSTRACTS



MEETING CHAIRMEN

**Professor Antonis Makrigiannakis –
Professor Timur Gürgan**

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Invited Speakers

GREEK

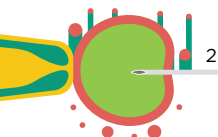
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Vlaisavljevic Veljko SLOVENIA
Watrelot Antoine FRANCE



Dear Colleagues and Friends,

On behalf of the Organizing Committee, we have the pleasure to welcome you all to the **XV Annual Meeting of the Mediterranean Society for Reproductive Medicine** which will be held from the **19th to the 21st October 2018, at the IBIS STYLES Heraklion Central Hotel** in Crete.

We are confident that the **XV Annual Meeting of the Mediterranean Society for Reproductive Medicine will serve as a unique opportunity for all participants to deepen their knowledge and expertise in a wide array of topics of Reproductive Medicine.**

It will also enable the MSRM community to disseminate its scope and mission further and to attract a growing number of members and affiliated societies within the International Human Reproduction Society.

To this end, we have already secured exceptional speakers to hold presentations on the following topics:

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

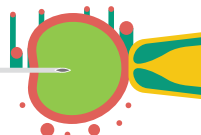
We look forward to welcoming you all and to sharing a unique scientific and cultural experience.



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



Professor Gürgan Timur MD
President, MSRM
Meeting Chairman



HALL A

R E G I S T R A T I O N S

09.00

10.00-14.00

HOT TOPIC I:

“TUBAL SURGERY – EXTRAUTERINE PREGNANCY”

Chairs: A. Watrelot – V. Tanos

Hy-Co-Sy : The role in tubal infertility. S. Mousourakis

3D scan and endoscopy: the complementary tools for tubal infertility. V. Tanos

Tubal recanalization after sterilization. A. Watrelot

Best option for ectopic pregnancy: to operate or not? V. Tanos

A new chapter of tubal pathology: the subtle tubal lesions and their impact on infertility. A. Watrelot

Role of hysteroscopy in diagnostic and treatment of tubal pathology. T. Motrenko

The influence of hydrosalpinx on ART outcome. A. Makrigiannakis

What to do in case of hydrosalpinx? A. Watrelot

ART after tubal surgery. A. Makrigiannakis

14.00-15.00

LUNCH BREAK

15.00-16.00

ORAL PRESENTATIONS

Chairs: M. Rasidaki – A. Pontikaki

O.P. 1 Study of apoptotic genes in the in vitro maturation of mouse oocytes in the presence and absence of CRH.

D. Mavrogianni, A. Drakoulia, S. Stavrou, D. Loutradis, P. Drakakis
Molecular Biology of Reproduction Unit, Assisted Reproduction Division, 1st Ob/Gyn Dept, Medical School, National and Kapodistrian University of Athens, Greece

O.P. 2 Association of ARG72PRO polymorphism and recurrent abortions in a greek population

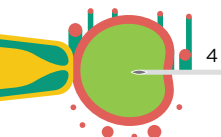
S. Stavrou, D. Dedousi, D. Mavrogianni, D. Loutradis, P. Drakakis
Molecular Biology of Reproduction Unit and Recurrent Abortions Unit, Assisted Reproduction Division, 1st Ob/Gyn Dept, Medical School, National and Kapodistrian University of Athens, Greece

O.P. 3 Caesarian scar pregnancy: A case report

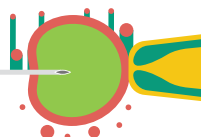
V. Christoforaki, I. Kokolakis, F. Makrigiannakis, E. Kouvidis, A. Pontikaki, A. Makrigiannakis
University Hospital of Heraklion, Department of Obstetrics and Gynecology

O.P. 4 Ovarian cancer during pregnancy, diagnostic challenges

I. Drakakis, I. Kokolakis, V. Christoforaki, A. Karamani, A. Makrigiannakis
University Hospital of Heraklion, Department of Obstetrics and Gynecology



HALL B	
REGISTRATIONS	
09.00	
10.00-14.00	<p>HOT TOPIC II: “MSRM DIPLOMA IN CLINICAL ASSISTED REPRODUCTION PART I” Chairs: H. Sallam - A. Makrigiannakis</p> <p>Basic course (1 day) and MCQ examination.</p> <ol style="list-style-type: none"> 1. Introduction and history of assisted conception. H. Sallam 2. Ovulation, fertilization, implantation. A. Makrigiannakis 3. Stimulation protocols. I. Messinis 4. Ultrasound monitoring and oocyte retrieval. T. Motrenko 5. Sperm preparation. C. Manna 6. Laboratory aspects of assisted reproduction. B. Kovacic 7. IUI – clinical aspects. T. Gürgan 8. IVF and ICSI – clinical aspects. V. Vlasisavljevic 9. Embryo transfer. H. Sallam
14.00-15.00	LUNCH BREAK
15.00-16.00	<ol style="list-style-type: none"> 10. Luteal phase support. O. Sefrioui 11. Cryopreservation. B. Kovacic 12. PGD. D. Daphnis 13. MCQ examination – results revised and announced locally.
20.00	OPENING CEREMONY & WELCOME RECEPTION



HALL A

15.00-16.00

- O.P. 5** An audit on management of threatened preterm labour in obstetrics and gynaecology
 V. Michopoulou, V. Mytaras, G. Spiliopoulos, T. Karypidis, S. Patramani, A. Makrigiannakis
University Hospital of Heraklion, Department of Obstetrics and Gynecology
- O.P. 6** Early onset severe fetal anemia due to rhesus d alloimmunization in a pregnancy with prior history
 S. Neonakis, M. Goula, V. Michopoulou, K. Krithinakis, A. Makrigiannakis
University Hospital of Heraklion, Department of Obstetrics and Gynecology
- O.P. 7** An audit to review the characteristics and management of placenta previa & placenta accreta spectrum at University Hospital of Heraklion, 2016- 2018.
 A. Pontikaki, S. Neonakis, I. Mikelopoulos, N. Verykokkou, M. Fourlan, A. Makrigiannakis
Department of Obstetrics & Gynecology, University Hospital of Heraklion, Crete, Greece

16.00-17.00

**SESSION I:
 "CONTROVERSIES IN IVF"**

Chairs: T. Motrenko – P. Karantzis

Commercialization of unproven technologies in reproductive medicine.
 V. Vlasisavljevic

Mitochondria as biomarker of implantation. B. Kovacic

Do we have any proof that boosting mitochondrial function in oocytes increases success? T. Ebner

17.00-18.30

**SESSION II:
 "FERTILITY PRESERVATION"**

Chairs: T. Gürgan – V. Vlasisavljevic - E. Vardaki

Updated of fertility preservation results. P. Barri

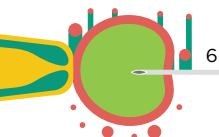
CIN 2-3 in pregnancy. Observation or LLETZ in first trimester? E. Paraskevaidis

Fertility preservation in cancer patients. The role of the gynecologic oncologist.
 A. Rodolakis

Fertility Preservation in non cancer patients. The role of reproductive specialist.
 P. Drakakis

20.00

OPENING CEREMONY & WELCOME RECEPTION



HALL A

08.00-09.00

ORAL PRESENTATIONS

Chairs: T. Vrekoussis - M. Asmarianaki - Aik. Stefanaki

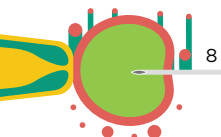
- O.P. 8** Reinke's crystals in perivascular and peritubular leydig cells in men with azoospermia
 D. Ježek¹, D. Pavičić Baldani², M. Kordić³
¹Departments of Histology and Embryology & Transfusion Medicine and Transplantation Biology, University Hospital Zagreb, University of Zagreb, School of Medicine, Zagreb, Croatia, ²Clinic for Gynaecology and Obstetrics, University Hospital Zagreb, University of Zagreb, School of Medicine, Zagreb, Croatia, ³Clinic for Urology, University Hospital Mostar, University of Mostar, School of Medicine, Bosnia and Herzegovina
- O.P. 9** Re-evaluation of semen preparation techniques in the aspect of DNA maturity and oocyte activation factor in addition to ultrastructure and routine semen analysis.
 E. Kervancioğlu Demirci¹, M.E. Kervancioglu²
¹Histology and Embryology Department, Istanbul Faculty of Medicine, Istanbul University, Istanbul, TURKEY, ²IVF Unit, Obstetrics and Gynaecology Department, Cerrahpaşa Faculty of Medicine, Istanbul University, Istanbul, Turkey
- O.P. 10** Study of the expression of CRH receptors,CRH-R1 and CRH-R2 in the development stage of blastocyst in mice.
 K. Kouvoutsaki, V. Dinopoulou, D. Mavrogianni, P. Drakakis, D. Loutradis
IVF Unit, ¹Department of Obstetrics and Gynecology of Athens University Medical School
- O.P. 11** Fragile X premutations in greek women with primary ovarian insufficiency
 P. Messaropoulos¹, C. Sofocleous², M. Oikonomou¹, C.V. hatzidakis¹, S. Neofytou¹, N. Salakos¹, N. Vrachnis¹, E. Deligeoroglou¹, A. Makrigiannakis³, E. Frysira², S.N. Kalantaridou¹
¹Unit on Primary Ovarian Insufficiency, 2nd Department of Obstetrics & Gynecology, University of Athens School of Medicine, "Aretaleion" Hospital, Athens, Greece; ²Department of Medical Genetics, Choremio Research Centre, ³Department of Pediatrics, University of Athens School of Medicine, Athens, Greece; ³Department of Obstetrics & Gynecology, University of Crete School of Medicine, Heraklion, Greece
- O.P. 12** Findings in women with recurrent postmenopausal bleeding investigated with hysteroscopy
 M. Nikolaou, D. Kosta, G. Andreadakis, K. Ntzelepis, T. Katasos
Department Of Obstetrics & Gynecology, General Hospital Of Agios Nikolaos, Agios Nikolaos, Crete, Greece
- O.P. 13** Endoscopic management of a case of unilateral pyometra secondary to klebsiella
 M. Nikolaou, D. Kosta, G. Andreadakis, K. Ntzelepis, T. Katasos
Department of Obstetrics & Gynecology, General Hospital of Agios Nikolaos, Agios Nikolaos, Crete, Greece
- O.P. 14** Age-related changes in endometrial cell function and differential gene expression that affect receptivity of human endometrium.
 S. Zafiropoulou, Aik. Verdiaki, F. Makrigiannakis, A. Makrigiannakis
University Hospital of Heraklion, Department of Obstetrics and Gynecology

09.00-09.30

KEY NOTE LECTURE

Chairs: T. Motrenko - M. Paschopoulos

The hysteroscopic digital clinic. R.Campo



HALL B

09.30-12.00 **HOT TOPIC III:**
«EMBRYOLOGY: Blastocyst biopsy: from theory to practice»
Chairs: L. Rienzi - B. Balaban

09.30-12.30

THEORY

09.30-10.00

New insights in embryology. L. Rienzi

10.00-10.30

Genetics in IVF. D. Cimadomo

11.00-11.30

Embryo morphology assessment. T. Ebner

11.30- 12.00

Blastocyst stage culture and assessment. B. Balaban

12.00-12.30

COFFEE BREAK

12.30-14.00

12.30 -13.00

Artificial blasocoel collapse of human blastocysts before vitrification. B. Kovacic

13.00 – 13.30

Discussion.

13.30 -14.00

Embryo development and assessment (A').

14.00-15.00

LUNCH BREAK

15.00-16.30

15.00 -15.30

Embryo development and assessment (B').

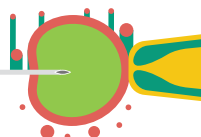
15.30 - 16.00

PRACTICE

(Video and interactive session with the panel).

16.00 - 16.30

Blastocyst biopsy: tips and tricks.



HALL A

09.30-10.30

SESSION III: «EXPERTS INTERACTION»

Moderator: A. Makrigiannakis

Experts Panel: T. Ebner, R. Campo, L. Gianaroli, I. Messinis, D. Baldani

- Time Lapse. Is it worth?
- Hysteroscopy to all before IVF or by indication?
- Should mosaic embryos be transferred? Risks of the new born?
- PCOS: individualization of treatment. How?
- Evidence – based luteal support: What, when and how long?
- Bad quality of embryos? Is it the lab or the stimulation?
- What to do with RIF?

10.30-12.00

SESSION IV: “INCREASING ENDOMETRIAL RECEPTIVITY”

Chairs: D. Loutradis – P. Barri

The impact of uterine microbiome. T. Gürgan

The embryo in RIF: genetic selection and strategies for improving its implantation potential. L. Gianaroli

Hysteroscopic value in the diagnosis of adenomyosis. R. Campo

Molecular Insights of Aging in Human Embryo Implantation. A. Makrigiannakis

12.00-12.30

COFFEE BREAK

12.30-13.15

SYMPOSIUM - FERRING

Translating evidence in clinical practice: The pathway of tomorrow.

Chairs: A. Makrigiannakis - S. Kalantaridou

The daily practice in COS: Evidence or intuition? E. Makrakis

Predicting the response in ART: The biomarkers lead the way. N. Vlachos

13.15-14.00

SYMPOSIUM - MERCK SERONO

Individualization and precision in IVF

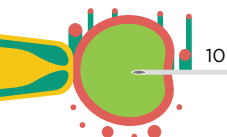
Chairs: M. Mastrominas - I. Giakoumakis

Origin and evolution of gonadotrophins. M. Tsigotis

Optimize FSH & LH in IVF protocols. K. Kostaras

14.00-15.00

LUNCH BREAK



HALL B

16.30-18.00

SYMPOSIUM DELLA SOCIETA ITALIANA DELLA RIPRODUZIONE UMANA (SIRU)

Chairs: C. Manna - H. Sallam

Consecutives Ejaulates in IVF. Possible improvements. C. Manna

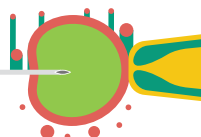
Fertility and ovarian ageing. S. Luisi

Should PGT-A be offered to all patients? S. Chamayou

Should hysteroscopy be performed in all patients before IVF? P. Inaudi

18.00-18.30

COFFEE BREAK



HALL A

15.00-16.30

SESSION V: "ENDOMETRIOSIS - ADENOMYOSIS"

Chairs: A. Watrelot - K. Zikopoulos - R. Pabuccu

Diagnosis of Endometriosis: What is new? K. Dafopoulos

Removal of Endometrioma before IVF. Where is the evidence? O. Sefrioui

How can surgery improve fertility in adenomyosis? G. Grimbizis

Surgical management of cesarean scar defect (Niche) before further fertility.

V. Tanos

16.30 -18.00

SESSION VI:

"CONTROVERSIAL ISSUES"

Chairs: B. Tarlatzis - P. Barri - Y. Şahin

Blastocyst versus cleaved embryo transfer: do we have enough evidence?

M. Aboulghar

In vitro maturation (IVM) - impact on embryos' and children's development.

T. Strowitzki

Optimizing Endometrial receptivity. The role of progesterone on the day of the final oocyte maturation. D. Baldani

Conservative treatment of fibroids. J. Donnez

18.00 -18.30

COFFEE BREAK

18.30-19.00

SATELLITE LECTURE - FARAN

Chair: N. Nikolettos

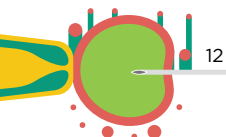
Epigenetic role of mitochondria: evidence driven speculations. M. Dattilo

19.00-19.30

KEY NOTE LECTURE

Chairs: H. Sallam - J.M. Dreyfus

A vision into the future of Reproductive Medicine. M. Aboulghar



HALL A

08.00 -09.00

ORAL PRESENTATIONS

Chairs: M. Rasidaki - E. Ziogos - G. Anifantis

O.P. 15 Clinical exome sequencing: deciphering the genetic grounds of unexplained infertility.

P. Constantoulakis¹, A. Argyriou², D. Dafnis², I. Giakoumakis², C. Costaras³, F. Georgiakodis⁴, K. Oikonomaki⁵, G. Christopoulou⁵
¹Bioanalytica-Genotype Sa., Athens, Greece, ²Mediterranean Fertility Institute, Chania, Creta, Greece, ³Institute of Life Ivf Center, Athens, Greece, ⁴University of Piraeus, Dept. of Biostatistics, Piraeus, Greece, ⁵Science Labs Medical Institute, Athens, Greece

O.P. 16 HPV E6/E7 mRNA expression compared to HPV DNA in Greek population increases the specificity and positive predictive value of cervical cancer screening.

S.P. Derdas^{1,2}, S.K. Archondakis^{2,3}, R.S. Oustambasidou², D.A. Spandidos¹
¹Laboratory of Clinical Virology, Medical School, University of Crete, Heraklion; ²Alpha Prolipsis Cytopathology Laboratories, Athens. ³401 General Military Hospital of Athens

O.P. 17 Polycystic ovary syndrome as a risk factor for premature ovarian insufficiency: controversial data.

C. Pagkaki, A. Kontogewrgi, E. Fitsakis, E. Kouvidis, E. Ziogos, A. Makrigiannakis
 University Hospital of Heraklion, Department of Obstetrics and Gynecology

O.P. 18 Vulvar angiomyofibroblastoma. A rare clinical and surgical tumor.

C. Goudeli, E. Kouvidis, S. Patramani, F. Makrigiannakis, C. Pagkaki A. Makrigiannakis
 University Hospital of Heraklion, Obstetrics-Gynecology, Iraklio- Crete, Greece

O.P. 19 Pemphigus vulgaris in pregnancy. A case report.

I.Kokolakis, D. Koutroulakis, D. Koumaki, S. Kruger, K. Krasagakis, A. Makrigiannakis
 University Hospital of Heraklion, Department of Obstetrics and Gynecology

O.P. 20 Non-operative management of splenic pregnancy with selective embolism and methotrexate

V. Mytaras, S. Patramani, I. Drakakis, D. Tsetis, M. Raisaki, A. Makrigiannakis, Th. Vrekoussis, F. Makrigiannakis
 University Hospital of Heraklion, Department of Obstetrics and Gynecology

O.P. 21 Assesment of uterine cavity by hysteroscopy in infertile women with recurrent pregnancy loss and recurrent IVF failures (RIF).

M. Nikolaou, D. Kosta, G. Andreadakis, K. Ntzelepis, T. Katasos
 Department of Obstetrics & Gynecology, General Hospital of Agios Nikolaos, Agios Nikolaos, Crete, Greece

09.00-09.30

KEY NOTE LECTURE

Chair: T. Grgan

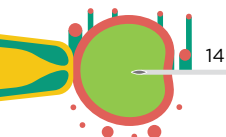
Ovarian Tissue reimplantation. The future of HRT? J. Donnez

09.30-10.00

SATELLITE LECTURE - ANGELINI PHARMA

Chair: A. Makrigiannakis

The controversy of LH activity in COS. To be or not to be? E. Kolibianakis



HALL B

10.00-11.30

TURKISH SESSION

Chairs: Ö. Moraloglou - C. Gülerman

Isthmocele and fertility: Fact or Fiction?

H. Görkemli

The place of random start ovarian stimulation in ART: How, when?

M. Sönmezer

Assesment of endometrium during ovarian stimulation: Is it necessary?

E.N. Tavmergen Göker

Luteal phase support in ART: Recent understanding and practice.

B. Baysal

Embryo transfer: Is there a best technique?

C. Fıçıcıoğlu

Surgery Before IVF Cycles: Do they increase the success rates?

R. Pabuçcu

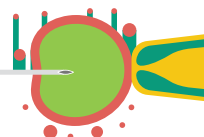
11.30-12.00

COFFEE BREAK

14.00-15.00

OPEN DISCUSSION - CONCLUSIONS

A. MAKRIGIANNAKIS



HALL A

10.00-11.30

SESSION VII: "CONTROVERSIAL ISSUES"

Chairs: K. Zikopoulos - A. Daponte

Novel aspects in the endocrinology of the menstrual cycle. I. Messinis

Freeze all for all? B. Tarlatzis

HPV infection and Infertility. T. Agorastos

ART and longterm effects to the offsprings. D. Loutradis

11.30-12.00

COFFEE BREAK

12.00-13.00

SESSION VIII: "PREECLAMPSIA"

Chairs: A. Daponte - S. Sifakis

Should we screen for preeclampsia. What for? A. Antsaklis

Preeclampsia - a cardiac disease? M. Marketou

Preeclampsia and HELP. What is the difference? A. Athanasiadis

13.00-14.00

SESSION IIX: "ADOLESCENCE GYNECOLOGY"

Chairs: I. Messinis - P. Drakakis

How to prevent and or treat uterine bleeding problems? E. Deligeoroglou

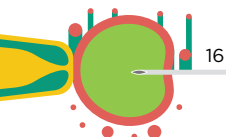
Contraception in adolescence. G. Creatsas

Contraceptives and thrombotic risks: What is the true risk? S. Kalantaridou

14.00-15.00

OPEN DISCUSSION - CONCLUSIONS

A. MAKRIGIANNAKIS



General Information



CRETE

Crete is the place where myths look like history and history is like a myth. Crete is the largest island in Greece, and the fifth largest one in the Mediterranean Sea. Here, you can admire the remnants of brilliant civilizations, explore glorious beaches, impressive mountainscapes, fertile valleys and steep gorges, and become part of the island's rich gastronomic culture.

VENUE

The Meeting will be held in IBIS STYLE Heraklion Central Hotel.
Koroneou 26, 71202
Heraklion Crete
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Fax: +30 2810 28 20 22

DATES

The Meeting will be held on 19-21 October 2018.

LANGUAGE

ENGLISH is the official language of the Meeting

SCIENTIFIC PROGRAM

The Scientific Program comprises of state-of-the-art Presentations, Round Table discussions, Lectures, Case Studies, Oral and Poster Presentations.

CME CREDITS

The meeting has been awarded 21 CME CREDITS by the Hellenic Medical Association.

SCIENTIFIC PRESENTATIONS AND PC RECEPTION

The Meeting Hall offers full audio-visual equipment. A PC Reception desk will be in place next to the Meeting Hall. All presentations should be clearly labeled with the author's name and session's title. All speakers are kindly requested to **check-in and deliver their presentations at least 2 hours prior to the session they participate.**

CERTIFICATE OF ATTENDANCE

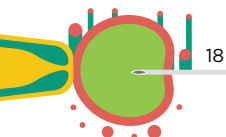
A certificate of attendance will be given to each registered participant at the end of the Meeting.

SECRETARIAT AND HOSPITALITY DESK

The Meeting Secretariat will operate during Meeting hours at the Meeting Hall Lobby.

LETTER OF INVITATION

Persons that require invitation letter for VISA purposes may refer directly to the Meeting Secretariat at info@msrmsociety.com. This procedure aims to assist participants who need to obtain a visa or permission to attend the Meeting and should not be considered as an official invitation covering fees or other expenses.



PASSPORT & VISAS

A valid passport is required for entry into Greece. Please consult the nearest Greek Consulate for specific details.

TRAVEL TO CRETE

There are daily flights to Heraklion international airport from almost all European cities. International delegates may need to fly via Athens (50 minutes flying time Athens to Heraklion). Heraklion has also daily ferryboat connections with Piraeus (approximately 7hrs trip). Please book your flights on time with Meeting Secretariat, ERA Ltd.

ELECTRIC POWER

Electric current in Greece is 220 / 240 AC / 50 Hz. The plugs have or round pins similar to those in many European countries.

LIABILITY AND INSURANCE

The Organizers cannot be held responsible for any claim concerning liability, personal damage, lost, theft, illness, non-appearance of speakers etc. We recommend participants and exhibitors to cover these risks by a respective insurance. The Program is subject to change without notice. In case of cancellation of the event the registration fees will be refunded. No additional claims will be prior accepted.

TRADE EXHIBITION

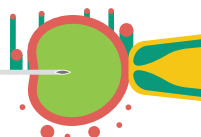
An exhibition of scientific products, pharmaceuticals, medical, instruments, equipment and relevant materials will be organized at the Meeting Venue.

DCART DIPLOMA MSRM

The Mediterranean Society for Reproductive Medicine (MSRM) announces the launch of its Diploma in clinical assisted reproduction (DCART).

The faculty consists of international experts in all aspects of assisted reproduction.

For more information visit www.Msrmsociety.com/Diploma



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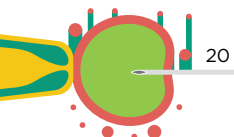
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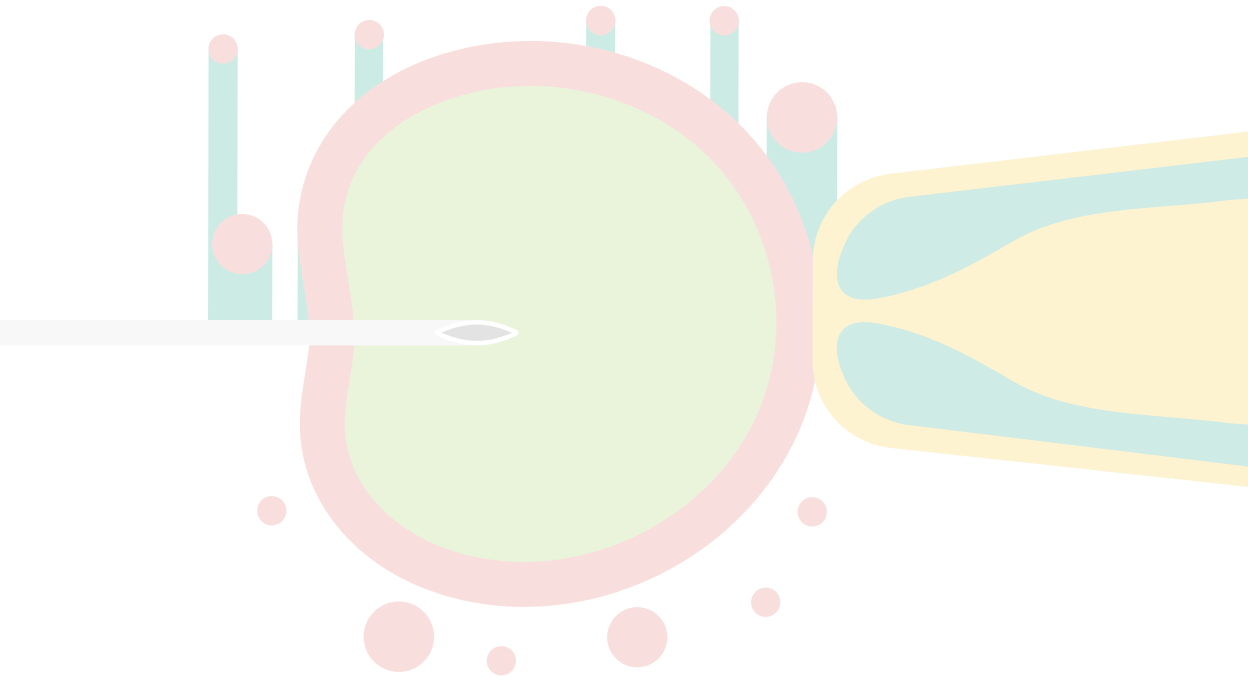


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ABSTRACT BOOK

Oral Presentations



MSRM
XV Annual Meeting
of the Mediterranean Society for Reproductive Medicine

O.P. 1

STUDY OF APOPTOTIC GENES IN THE IN VITRO MATURATION OF MOUSE OOCYTES IN THE PRESENCE AND ABSENCE OF CRH

D. Mavrogianni, A. Drakoulia, S. Stavrou, D. Loutradis, P. Drakakis

*Molecular Biology of Reproduction Unit, Assisted Reproduction Division, 1st Ob/Gyn Dept, Medical School, National and Kapodistrian University of Athens, Greece
Accredited Training Centre for Obstetrics & Gynecology by
the European Board & College of Obstetrics and Gynecology (EBCOG)*

Background: CRH receptors are present in uterus, placenta, and ovary. Ovarian CRH is involved in follicular maturation. Apoptosis is a process of programmed death of cells also present in somatic and germ cells in the ovary. As far as CRH is concerned, it has been shown that its receptors cannot initiate directly the activation of the mechanisms of apoptosis.

Aim: To investigate if the presence and/or absence of CRH influences the apoptotic genes *FasI*, *Bcl2*, *Bax* and *Casp3* during in vitro maturation.

Methods: Preantral follicles from 12 prepubertal female mice, were isolated and cultured in control media and in CRH 10^{-7} mol/liter. Total RNA was extracted and the expression of genes *FasI*, *Bcl2*, *BAX*, *Casp3* was assessed by real-time RT-PCR.

Results: *FasI* mRNA was not detected at all. *Bcl2* and *Bax* expressions had a statistically significant increase ($p < 0.05$) in the presence of CRH. Although an increase was found between control and CRH group for *Casp3*, no statistically significant difference was shown ($p > 0.05$).

Summary/Conclusions: The presence of CRH in the ovary and the suggested CRH-induced inhibition of oocyte maturation might be responsible for acute or chronic stress-related anovulation states. Expression of *Bcl-2* and *Bax* may be important in the maintenance of the number of oocytes and primordial follicles. Our findings indicated that CRH inhibits in vitro maturation of mouse oocytes by increasing the expression of pro-apoptotic genes.

O.P. 2

ASSOCIATION OF ARG72PRO POLYMORPHISM AND RECURRENT ABORTIONS IN A GREEK POPULATION

S. Stavrou, D Dedousi., D. Mavrogianni, D. Loutradis, P. Drakakis

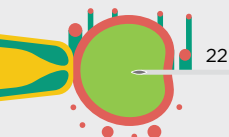
*Molecular Biology of Reproduction Unit and Recurrent Abortions Unit, Assisted Reproduction Division, 1st Ob/Gyn Dept, Medical School, National and Kapodistrian University of Athens, Greece
Accredited Training Centre for Obstetrics & Gynecology by
the European Board & College of Obstetrics and Gynecology (EBCOG)*

Background: *p53* is a tumor suppressor gene which plays a pivotal role in regulating the cell cycle, apoptosis and protecting the genome from DNA damage. Polymorphisms have been proposed as a probable cause which could increase the chances of miscarriage in otherwise healthy women. Recent studies provide evidence that the Arg72Pro single nucleotide polymorphism (SNP) at codon 72 of *p53* gene, is associated with the occurrence of idiopathic recurrent pregnancy loss (RPL).

Aim: This study was conducted to further investigate the association between the Arg72Pro (rs1042522) polymorphism and idiopathic recurrent pregnancy loss in a Greek population.

Methods: DNA was extracted from 74 cases of RPL and 48 controls. Genotyping was performed by PCR amplification of the *p53* Arg and Pro variants at codon 72. PCR results were visualized by using agarose gel electrophoresis.

Results: In the recurrent pregnancy loss group, the Arg72Pro polymorphism was detected in 28 out of 74 women (37, 8%). In the control group 5 out of 48 women (10, 4%) presented an Arg to Pro amino acid substitution.



Summary/Conclusions: We have investigated the association between a polymorphic site in the proline-rich region of the human p53 gene and the occurrence of IRM. Our results indicate that women carrying the Pro allele have a significantly higher risk of IRM than women with the Arg allele. Our findings may propose the hypothesis that changes of the proline-rich region of p53 could alter the potential of the protein to regulate processes in cell apoptosis or cell cycle arrest.

References

Pietrowski D, Bettendorf H, Riener EK, Keck C, Hefler LA, Huber JC, Tempfer C. Recurrent pregnancy failure is associated with a polymorphism in the p53 tumour suppressor gene. *Hum Reprod.* 2005 Apr;20(4):848-51. Epub 2004 Dec 17. PubMed PMID: 15608028.

Goodman C, Jeyendran RS, Coulam CB. P53 tumor suppressor factor, plasminogen activator inhibitor, and vascular endothelial growth factor gene polymorphisms and recurrent implantation failure. *Fertil Steril.* 2009 Aug;92(2):494-8. doi: 10.1016/j.fertnstert.2008.07.022. Epub 2008 Sep 30. PubMed PMID: 18829023.

O.P. 3

CAESARIAN SCAR PREGNANCY: A CASE REPORT

V. Christoforaki, I. Kokolakis, F. Makrigiannakis, E.Kouvidis, A.Pontikaki, A. Makrigiannakis

*University Hospital of Heraklion, Department of Obstetrics and Gynecology
 Accredited Training Centre for Obstetrics & Gynecology by
 the European Board & College of Obstetrics and Gynecology (EBCOG)*

Aim: Ectopic caesarian scar pregnancy (CSP) is considered to be the rarest form of ectopic pregnancy with catastrophic sequelae. Due to the increasing number of caesarian sections the prevalence of caesarian scar pregnancies has been raised in the recent years.

Materials and Methods: The patient, with a history of a previous caesarian section 4 years ago, presented in A & E with PV bleeding and lower abdominal pain. The transvaginal U/S revealed a gestation sac implanted on the site of the caesarian scar tissue. . In our management approach, 4 weeks after treating our patient with systemic multi-dose protocol of methotrexate administration alternating with leucovorine and suction evacuation of products of conception.

Results: As a rare condition, there are no specific guidelines nor consensus for the management of CSP. B-HCG went back to normal values with no adverse effects in the patient. The patient was followed up with serial β -HCG's and serial TVS.

Conclusions: There is an unmet need to define the guidelines for the diagnosis and management of CSP. As a high risk pregnancy with potential fatal complications, all women with previous caesarian sections need to be monitored and screened for CSP early in the first trimester of pregnancy to prevent associated complications.

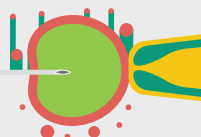
O.P. 4

OVARIAN CANCER DURING PREGNANCY , DIAGNOSTIC CHALLENGES

I. Drakakis, I. Kokolakis, V. Christoforaki, A. Karamani, S. Zafiropoulou, A. Makrigiannakis

*University Hospital of Heraklion, Department of Obstetrics and Gynecology
 Accredited Training Centre for Obstetrics & Gynecology by
 the European Board & College of Obstetrics and Gynecology (EBCOG)*

Introduction: It is rare to find an ovarian tumor or mass during pregnancy. One study estimates that only 2.4 - 5.7% of pregnancies will present with an ovarian mass. If an ovarian tumor is found, it is again rare that the mass is malignant (cancerous). The study above mentions that of these masses , only about 5% are expected to be malignant.



Case presentation: We present the case of a 31y old female in her second pregnancy with severe ovarian cancer symptoms, during the 32nd week of her pregnancy, which were initially misdiagnosed for pre-eclampsia.

Symptoms started earlier during the second trimester of the pregnancy with abdominal pain when they were misdiagnosed for contractions. The patient was transferred to our hospital at the 32nd week of her pregnancy with epigastralgia, edemas, dyspnoea, oliguria, pleural effusions, ascites, positive urine spot for protein, elevated blood pressure and elevated liver enzymes count and an emergency caesarean section was performed with the indication of pre-eclampsia. Intraoperative a sizeable formation of the right ovary was found and abdominal fluid was taken for cytological exam. The exam revealed evidence for ovarian adenocarcinoma while the patient transferred to the ICU due to her clinical condition deterioration with uncontrolled fluid loss, edemas, electrolyte imbalance, dyspnoea and peritoneal fluid infection. Full body CT & MRI scan revealed lymph node dispersion of the disease with a high suspicion for breast and peritoneal metastases. An axillary lymph node biopsy was taken and chemo therapy with carboplatin and paclitaxel started but the patient passed out a few days later.

Discussion: The aim of this case report is to raise clinical suspicion for further imaging and investigation for every abdominal discomfort during pregnancy that cannot definitely attributed to a cause.

O.P. 5

AN AUDIT ON MANAGEMENT OF THREATENED PRETERM LABOUR IN OBSTETRICS AND GYNAECOLOGY DEPARTMENT OF UNIVERSITY HOSPITAL OF HERAKLION, CRETE

V. Michopoulou, V. Mytaras, G. Spiliopoulos, T. Karypidis, S. Patramani, A. Makrigiannakis

University Hospital of Heraklion, Department of Obstetrics and Gynecology

Accredited Training Centre for Obstetrics & Gynecology by

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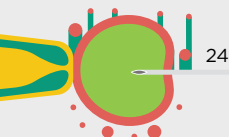
Background: In Europe, preterm delivery is defined as delivery after 22 completed weeks but before 37 weeks of gestation. Preterm birth worldwide has an incidence of around 5–8% and is responsible for 75% of perinatal deaths. The etiology of the syndrome is multifactorial including maternal, placenta and embryonic competition. Numerous risk factors have been listed providing prognostic value for pregnancies in high risk for preterm labour. There are many tocolysis protocols followed worldwide in terms of delaying labour, in order steroids to be administered.

Aims: To evaluate the efficacy of treatment protocols followed in threatened preterm labour and detect our weaknesses in terms of improving our clinical practice.

Methods: Data from 50 women hospitalized for reasons of threatened preterm birth were collected. Admission diagnosis included contractions, cervix inadequacy and premature rupture of membranes. Demographic data, medical history, risk factors, infections, pathologies in current pregnancy, treatment followed and outcome were recorded.

Results: Most women were hospitalized due to contractions. 44% in time of admission were in 30–34th week of pregnancy. Only 8% had history of preterm birth in a previous pregnancy. All women started tocolysis treatment and completed steroids administration. 18% reached full term pregnancy, 10% had preterm labour before 30w and 40% delivered between 34–37 weeks.

Conclusions: Data concerning the efficacy of tocolysis protocol used are encouraging. The weaknesses of our unit were observed in recording and evaluating women in high risk of preterm birth. Our plan is to improve practices followed, especially focusing on prolepsis and punctual response and readmit.



O.P. 6

EARLY ONSET SEVERE FETAL ANEMIA DUE TO RHESUS D ALLOIMMUNIZATION IN A PREGNANCY WITH PRIOR HISTORY

S. Neonakis, M. Goula, V. Michopoulou, K. Krithinakis, A. Makrigiannakis

*University Hospital of Heraklion, Department of Obstetrics and Gynecology
Accredited Training Centre for Obstetrics & Gynecology by
the European Board College of Obstetrics and Gynecology (EBCOG)*

Introduction: Rhesus D positive fetuses of Rhesus D negative mothers are at risk of developing fetal anemia or hemolytic disease of the newborn. In pregnancies with prior complicated history caution should be kept for early onset severe fetal anemia.

Case Presentation: We present a case of a 39 years old rhesus negative pregnant woman with a history of an unexplained stillbirth at 38 weeks in her third pregnancy, who was referred to our department on the 23rd week due to fetal ascites. The indirect Coombs test showed high level of antibodies. Fetal Rhesus was positive, determined by cfDNA test in the 1st trimester. The mother was never administered anti-D Rhesus immunoglobulin. Ultrasound examination demonstrated severe ascites, cardiomegaly and placentomegaly additional to MCA-PSV>1.5 MoMs for gestational age. Overall, three intrauterine transfusions were performed on the 23rd, 25th and 30th week of pregnancy. At 33 weeks an alive and well neonate was delivered by a planned c-section.

Discussion: In women with known Rhesus D status negative whose prior pregnancy was complicated with severe fetal anemia MCA-PSV should be closely monitored from 16 weeks of gestation as severe anemia occurs earlier in gestation than in the prior pregnancy.

O.P. 7

AN AUDIT TO REVIEW THE CHARACTERISTICS AND MANAGEMENT OF PLACENTA PREVIA & PLACENTA ACCRETA SPECTRUM AT UNIVERSITY HOSPITAL OF HERAKLION, 2016-2018

A. Pontikaki, S. Neonakis, I. Mikelopoulos, N. Verykokkou, M. Fournal, A. Makrigiannakis

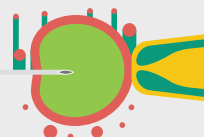
*Department of Obstetrics & Gynecology, University Hospital of Heraklion, Crete, Greece
Accredited Training Centre for Obstetrics & Gynecology by
the European Board College of Obstetrics and Gynecology (EBCOG)*

Introduction. Placenta previa (PP) and accreta spectrum (PAS) are important causes of bleeding in the second half of pregnancy and in labor and require a multidisciplinary approach to management. PP & PAS are challenging problems even for experienced Obstetricians & Gynecologists, as there is still no consensus about the optimal management with regard to the timing of delivery and the surgical approach.

Aim. We reviewed the characteristics and management of PP & PAS at the University Hospital of Heraklion to evaluate performance.

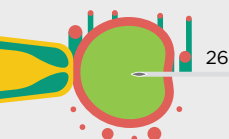
Material & Methods. Cases of confirmed placenta previa, accreta, increta and percreta were identified retrospectively from our hospital database. Medical records were carefully reviewed for maternal demographics, obstetric and gynecological history, imaging modalities, maternal complications and neonatal outcomes. Additional data regarding surgical management and intra-operative complications were collected from operative reports.

Results. In a two- year period (between 2016 and 2018) a total of 43 cases with PP and 8 cases with PAS were found. The majority of cases were complete previas and included 3 placenta accreta, 3 placenta increta and 2 placenta percreta. Most previas were posterior (25/43). Overall, most women were primigravidae (19/43) especially after infertility treatment (10/43) or secundigravidae (18/43) with a history of one previous cesarean section (15/43). More than half of women diagnosed with previa were over 35 years. Only one-third of cases (14/43) underwent complementary imaging by MRI to exclude PAS. Vaginal bleeding during hospitalization occurred in 11% of the patients. The majority of cases (89%) were electively delivered between 32 and 37 weeks. The cesarean section was performed under general anesthesia in 72% of cases. Ureteral stents were inserted preoperatively



in 46% of patients with major previa. Only 7 women (16%) with strong suspicion for PAS underwent a midline supraumbilical skin incision, while the rest (84%) had a Pfannenstiel incision. A fundal hysterotomy incision was chosen for 2 cases with placenta percreta. More than half of women required transfusion with at least 4 units of packed red blood cells (range 2- 10 Lt). In total, hysterectomy was performed only in 3 patients with PAS (7%), while 4 patients (9%) had bladder/ureteral injuries. There was one admission to the intensive care unit in a woman who presented transfusion- related acute lung injury after hysterectomy. Major postoperative complications were intra-abdominal infections (12%), ileus (3%) and second operation due to new bleeding (2%). Regarding neonatal outcomes, 38 babies were born preterm and needed admission to the neonatal intensive care unit. There was one in utero fetal death and one neonatal death.

Discussion. Our data show that the overall incidence is 3% for PP and 0.6% for PAS. In the population we reviewed, major risk factors for previa development were multiparity, history of one previous cesarean section, IVF pregnancy and maternal age over 35 years. Women underwent preterm planned delivery at a mean gestational age of 34 weeks. Surgical management has led to satisfactory results, as 93% of the patients preserved their uterus. Maternal and neonatal outcomes were also favorable in this audit. However, we have identified areas for improvement, which include modifying our surgical techniques to reduce intra-operative blood loss and reducing the cesarean birth rate at our hospital.



O.P. 8

REINKE'S CRYSTALS IN PERIVASCULAR AND PERITUBULAR LEYDIG CELLS IN MEN WITH AZOOSPERMIA

D. Ježek¹, D. Paviči Baldani², M. Kordić³

¹Departments of Histology and Embryology & Transfusion Medicine and Transplantation Biology, University Hospital Zagreb, University of Zagreb, School of Medicine, Zagreb, CROATIA, ²Clinic for Gynaecology and Obstetrics, University Hospital Zagreb, University of Zagreb, School of Medicine, Zagreb, CROATIA, ³Clinic for Urology, University Hospital Mostar, University of Mostar, School of Medicine, BOSNIA and HERZEGOVINA
 Accredited Training Centre for Obstetrics & Gynecology by the European Board College of Obstetrics and Gynecology (EBCOG)

Background: Reinke's crystals are regular structures found in human Leydig cells. It is speculated that these crystals could be a by-product of steroidogenesis. According to their location within the interstitial testis compartment, Leydig cells can be divided into perivascular (PVLc) and peritubular (PTLc).

Aim: To visualize and measure the presence of Reinke's crystals in PVLc and PTLc in patients with the preserved testis parenchyma (obstructive azoospermia cases, OA) and patients with non-obstructive azoospermia (NOA).

Material & Methods: A total of 110 testicular biopsies from infertile men (10 OA cases and 100 NOA patients) biopsied in the period 1998-2006 at the Clinic of Urology were used for histological and morphometric (stereological) analysis. Paraffin sections were stained with hemalaun and eosin and according to the modified Masson's method. Stereological analysis was performed using Weibel's multipurpose test system.

Results: Stereological analysis pointed out a decrease in the number of Reinke's crystals in NOA cases when compared to the control group (OA). The above-mentioned decrease was found both in PVLc and PTLc of NOA patients.

Conclusion: Based on the morphometric data, one can assume that in NOA cases Leydig cells somehow use Reinke's crystals for the production of androgens in order to respond to high levels of LH and to compensate the deficit of testosterone *in situ* needed for the restoration of spermatogenesis.

References: Soerensen RR, et al. Leydig cell clustering and Reinke crystal distribution in relation to hormonal function in adult patients with testicular dysgenesis syndrome (TDS) including cryptorchidism. *Hormones (Athens)*, 15(4):518-526, 2016

O.P. 9

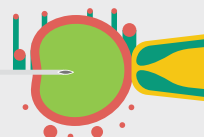
RE-EVALUATION OF SEMEN PREPARATION TECHNIQUES IN THE ASPECT OF DNA MATURITY AND OOCYTE ACTIVATION FACTOR IN ADDITION TO ULTRASTRUCTURE AND ROUTINE SEMEN ANALYSIS

E. Kervancıoğlu Demirci¹, M.E. Kervancıoğlu²

¹Histology and Embryology Department, Istanbul Faculty of Medicine, Istanbul University, Istanbul, TURKEY, ²IVF Unit, Obstetrics and Gynaecology Department, Cerrahpaşa Faculty of Medicine, Istanbul University, Istanbul, TURKEY
 Accredited Training Centre for Obstetrics & Gynecology by the European Board College of Obstetrics and Gynecology (EBCOG)

Background: Nowadays, assisted reproductive techniques (ART) are widely applied, but pregnancy rates per trial are around 40% and still under expectancy. Every step of ART needs to be reevaluated for higher success rates.

Aim: Sperm preparation is one of the major steps of ART procedure. Swim-up and density gradient washing (DGW) techniques are widely used for this purpose, and the efficacy is analyzed with routine semen analysis. The aim of this study is to evaluate and compare routine semen washing techniques and modified swim down



(MSD) technique with DNA maturity, ultrastructure, oocyte activation factor phospholipase C zeta (PLCZ) staining and patterns in addition to semen analysis.

Material & Methods: 37 patients applied to infertility clinic and 21 patients with a minimum sperm count of 10×10^6 /ml were included. Semen were prepared with MSD, swim-up and DGW, thereafter aniline blue staining, immunofluorescent stain of PLCZ, transmission electron microscopy (TEM) and routine semen analyses were performed.

Results: There was no significant difference between the techniques in sperm recovery rates and DNA maturity rates, but the highest motile sperms were recovered and the best PLCZ staining were observed by MSD, and the lowest morphologically normal sperm count was observed by DGW. TEM analyses showed clearly less tail abnormalities in swim-up and MSD.

Conclusion: MSD showed to select motile sperms and sperms with oocyte activation factor better than other methods. Nonsignificance of some parameters can be due to the small sample size. MSD used in this study is a promising method for routine ART.

O.P. 10

STUDY OF THE EXPRESSION OF CRH RECEPTORS, CRH-R1 AND CRH-R2 IN THE DEVELOPMENT STAGE OF BLASTOCYST IN MICE

K. Kouvoutsaki, V. Dinopoulou, D. Mavrogianni, P. Drakakis, D. Loutradis

*IVF Unit, 1st Department of Obstetrics and Gynecology of Athens University Medical School
Accredited Training Centre for Obstetrics & Gynecology by
the European Board College of Obstetrics and Gynecology (EBCOG)*

Background: Corticotropin-releasing hormone (CRH) is a 41 amino acid peptide, which stimulates corticotropes through the HPA (hypothalamus-pituitary-adrenals) axis. Two receptors have been found in human, CRH-R1 and CRH-R2, through whom CRH exerts its actions. CRH-R1 is expressed in different parts of woman reproductive system in both pregnant and non-pregnant stages¹. CRH-R1 has also been found in embryonic membranes¹. During the implantation the endometrium has inflammatory response characteristics, however the fetus is not rejected as a semi-allograft it is. During this procedure the role of Fas/FasL apoptotic pathway is of great importance as it removes the excess of T-lymphocytes leading to the acceptance of the fetus².

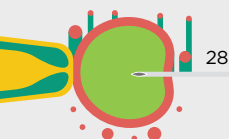
Aim: Assessing the expression of CRH receptors (CRH-R1 and CRH-R2) in mice in the development stage of blastocyst.

Material and methods: Total RNA was extracted from 200 mouse blastocysts and was assessed by the molecular technique of Real-Time PCR (SYBR GREEN method) for the expression of CRH-R1 and CRH-R2 mRNAs. G6PD expression levels were used as a control for the study.

Results: CRH-R1 mRNA is expressed in the development stage of blastocyst, whereas CRH-R2 mRNA is not expressed in this development stage.

Conclusion: CRH, through its receptor CRH-R1, induces the secretion of FasL (pre-apoptotic cytokine) at both decidua and trophoblast cells which activate Fas/FasL apoptotic pathway³. Dosaging antalarmin (CRH-R1 antagonist) in mice mice inhibits the procedure implantation³. Those, along with the study's results suggest an active role of CRH-R1 (expressed in fetus) in implantation.

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O.P. 11

FRAGILE X PREMUTATIONS IN GREEK WOMEN WITH PRIMARY OVARIAN INSUFFICIENCY

P. Messaropoulos,¹ C. Sofocleous,² M. Oikonomou,¹ V. Chatzidakis,¹ S. Neofytou,¹ N. Salakos,¹ N. Vrachnis,¹ E. Deligeorgiou,¹ A. Makrigiannakis,³ E. Frysira,² S.N. Kalantaridou¹

¹Unit on Primary Ovarian Insufficiency, ²nd Department of Obstetrics & Gynecology, University of Athens School of Medicine, "Aretaieion" Hospital, Athens, Greece; ²Department of Medical Genetics, Choremio Research Centre, ¹st Department of Pediatrics, University of Athens School of Medicine, Athens, Greece; ³Department 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: Fragile X syndrome (FRAXA) is a neurodevelopmental disorder that constitutes the most common cause of inherited mental retardation, autism and intellectual disabilities. FRAXA 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, while women with POI of unknown cause have a risk of 1/50 to be carriers of a permutation in the *FMR1* gene.

Aim: Our goal was to investigate the prevalence of the Fragile X premutations in women with POI, who were 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. The analysis was performed at the Choremeio Research Laboratory, Agia Sofia Children's Hospital.

Results: Fifteen women were referred for genetic analysis of the *FMR1* gene. The median age was 32.2 years. Three out of 13 women were fragile X permutation carriers. Two FMR1 results are pending.

Conclusions: Women with POI have a 5-10% chance of spontaneous pregnancy. The occurrence of fragile X permutation 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. 12

FINDINGS IN WOMEN WITH RECURRENT POSTMENOPAUSAL BLEEDING INVESTIGATED WITH HYSTEROSCOPY

M. Nikolaou, D. Kosta, G. Andreadakis, K. Ntzelepis, T. Katasos

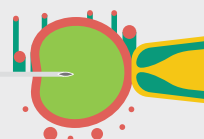
Department of Obstetrics & Gynecology, General Hospital of Agios Nikolaos, Agios Nikolaos, Crete, Greece

Accredited Training Centre for Obstetrics & Gynecology by the European Board College of Obstetrics and Gynecology (EBCOG)

Aim: The aim of this study is to assess the prevalence of endometrial pathology of patients presented with recurrent postmenopausal bleeding (PMB) after incorporation of hysteroscopic examination.

Material & Methods: Between November 2012 and July 2018, a total of 27 consecutive patients presenting with recurrent PMB to our regional hospital were underwent hysteroscopy. All patients underwent pelvic examination and ultrasound scanning. An endometrial biopsy with curettage was performed when endometrial thickness was >5 mm in patients with a first episode of PMB.

Results: The patients' ages ranged from 43 to 70 years (median was 54.7 years). The histological results from hysteroscopy were obtained from the pathology department. The majority of patients with recurrent PMB had endometrial polyp and atrophic endometrium (81.4%). Other diagnoses included submucous fibroid (7.4%) and endometrial hyperplasia (11.1%).



Conclusion: We concluded that all patients with recurrent PMB should be investigated thoroughly with hysteroscopy that allows precise diagnosis of various intrauterine pathologies. Recurrent PMB results in less likelihood of premalignant and malignant endometrial disease; however there are high incidences of endometrial polyps and submucous fibroids.

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O.P. 13

ENDOSCOPIC MANAGEMENT OF A CASE OF UNILATERAL PYOMETRA SECONDARY TO KLEBSIELLA

M. Nikolaou, D. Kosta, G. Andreadakis, K. Ntzelepis, T. Katasos

Department of Obstetrics & Gynecology, General Hospital of Agios Nikolaos, Agios Nikolaos, Crete, Greece

Accredited Training Centre for Obstetrics & Gynecology by

the European Board College of Obstetrics and Gynecology (EBCOG)

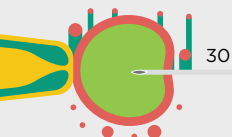
Background-Aim: Pyometra is an accumulation of pus in the uterine cavity. It represents 0.01-0.5% of gynaecological admissions. It mainly appears in postmenopausal women with an incidence as high as 13.6%, usually associated to malignant entities of the genital tract. The main complications of pyometra are bacteraemia and sepsis as well as the feared spontaneous uterine perforation with secondary generalised peritonitis.

Material & Methods: A patient 49 year old with recurrent low-grade fever and lower abdominal pain was admitted. During the clinical examination there was a strong sensitivity to the bimanual gynecological palpation and she was introduced for hospitalization due to pelvic inflammation disease. Ultrasonography revealed accumulation of fluid with incomplete uterine septum and fibrous septa in the uterine cavity. Leucocytosis with neutrophilia and elevated serum concentration of C-reactive protein were detected. The rest of the hematological, biochemical and coagulation studies were normal. A MRI scan confirmed the ultrasound findings, an intrauterine heterogeneous liquid collection, suggestive of pyometra in the right hemicavity. A hysteroscopy was performed with drainage of purulent material and resection of incomplete septa/fibrous intrauterine adhesions with endoscopic scissor. In endometrial fluid cultures *Klebsiella* spp. was isolated. The endometrial cavity was irrigated, and the patient was treated with antibiotics. The clinical course was favorable and she was asymptomatic 5 days later. The patient was discharged with an improved clinical picture and follow-up instructions per os.

Conclusion: Pyometra is an entity, which is generally associated with causes that produce interference in the natural drainage of the uterine cavity. Precise knowledge of mullerian anomalies is necessary in the management of these patients.

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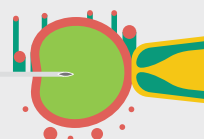
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O.P. 14

AGE-RELATED CHANGES IN ENDOMETRIAL CELL FUNCTION AND DIFFERENTIAL GENE EXPRESSION THAT AFFECT RECEPTIVITY OF HUMAN ENDOMETRIUM**S. Zafiropoulou, Aik. Verdiaki, F. Makrigiannakis, A. Makrigiannakis***University Hospital of Heraklion, Department of Obstetrics and Gynecology, Accredited Training Centre for Obstetrics & Gynecology by the European Board College of Obstetrics and Gynecology (EBCOG)*

Maternal age, in the developed world countries, has been steadily increasing over the years and is known to be the main cause of reduced reproduction success and a major risk factor for abnormal newborn development. The age-related reproductive decline in mammals is mainly attributed to the significant increase in oocyte chromosome segregation abnormalities. Recent studies, using animal models, have pinpointed that maternal age may be related with severe placentation defects and abnormal decidualization responses by the uterine stroma. Endometrium's decidualization process, its embryo receptivity and its role in embryo development is modulated by its environment. Changes in epithelial and stromal endometrium cell function, as well as changes in their gene and protein expression regulate the uterine environment and its characteristics. In our study, epithelial and stromal endometrium cell proliferation was investigated in relation to women's age. Endometrial biopsies from women undergoing hysterectomies were obtained, with informed consent. Tissues were cut, digested and filtered in order to separate the different cell populations - as described in previously published protocols. Epithelial and stromal endometrium cells were then cultured and either used in proliferation assays or collected for mRNA extraction in order to analyse gene expression using Real-time PCR. The expression of genes related to the decidualization process, cell proliferation and receptivity of the endometrium (BMP-2, Hoxa10, Hoxa11, E-Cadherin, STAT3) were associated with woman's age. The description of mechanisms and associated molecules that can affect the characteristics of the aging endometrium can aid to the understanding of the causes of reduced human fertility.



O.P. 15

CLINICAL EXOME SEQUENCING: DECIPHERING THE GENETIC GROUNDS OF UNEXPLAINED INFERTILITY**P. Constantoulakis¹, A. Argyriou², D. Dafnis², I. Giakoumakis², C. Costaras³, F. Georgiakodis⁴, K. Oikonomaki⁵, G. Christopoulou⁵***¹Bioanalytica-Genotype S.A., Athens, Greece, ²Mediterranean Fertility Institute, Chania, Creta, Greece, ³Institute of Life Ivf Center, Athens, Greece, ⁴University of Piraeus, Dept. of BioStatistics, Piraeus, Greece, ⁵Science Labs Medical Institute, Athens, Greece Accredited Training Centre for Obstetrics & Gynecology by the European Board College of Obstetrics and Gynecology (EBCOG)*

Background: The etiology of unexplained infertility is highly heterogeneous and besides all efforts, many couples remain undiagnosed. Most likely, idiopathic subfertility/infertility cases have a genetic background and may not be detected by standard investigations.

Aim: Clinical exome sequencing may unveil the genetic grounds of infertility, by sequencing in parallel, all genes known to be implicated in reproductive pathways.

Methods: For the implementation of Next Generation Sequencing, DNA was extracted from blood or swab samples of men and women with fertility issues. Subsequently, exons, exon/intron boundaries and regulatory elements of 4.900 clinically significant genes were capture-enriched using >150.000 probes designed by SOPHiA GENETICS against the human genome. Following sequencing, complex bioinformatics analysis was performed and variants were classified, according to database entries and peer reviewed literature (SOPHiA DDM platform).

Results: The gene spectrum analyzed was selected, mainly based on the Human Phenotype Ontology database. A total of 109 genes were included with either established correlation to infertility or a known role in reproductive pathways. From the 32 cases with unexplained infertility investigated 28 of them had either pathogenic or likely pathogenic variants.

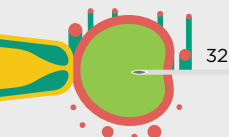
Summary/Conclusions: Traditional single-gene testing is time consuming, expensive and may be ineffective. Robust genomic methods, such as Next Generation Sequencing of the clinically significant exome, allow for simultaneous gene investigation of well-established causative genes along with others implicated in the female and male reproductive tracts. Thus, new technologies may overcome limitations, significantly contributing to optimum reproduction choices and the fittest IVF strategy to be applied to each couple.

O.P. 16

HPV E6/E7 MRNA EXPRESSION COMPARED TO HPV DNA IN GREEK POPULATION INCREASES THE SPECIFICITY AND POSITIVE PREDICTIVE VALUE OF CERVICAL CANCER SCREENING**S.P. Derdas^{1,2}, S.K. Archondakis^{2,3}, R.S. Oustambasidou², D.A. Spandidos¹***¹Laboratory of Clinical Virology, Medical School, University of Crete, Heraklion; ²Alpha Prolipsis Cytopathology Laboratories, Athens ³401 General Military Hospital of Athens Accredited Training Centre for Obstetrics & Gynecology by the European Board College of Obstetrics and Gynecology (EBCOG)*

Aim: Human papillomaviruses have been established as a risk factor for invasive carcinoma of the uterine cervix. HPV DNA detection provides an efficient method of screening. Detection of the HPV E6/E7 onco-gene expression emerged as a promising biomarker to determine the risk for the progression to high-grade cervical lesions. In the present study, we aimed to determine the HPV DNA positive and mRNA expression.

Material & Methods: We estimated the frequency of detection of different human papilloma virus (HPV) types in women with atypical squamous cells of undetermined significance (ASCUS) or low-grade squamous intraepithelial lesions (LSIL) cytology in a population-screening programme. 24 liquid-based cytology (LBC) samples were tested using real time PCR IVD Diagnostic kit, which detects 36 HPV types.



Results: 12.5 % of samples were positive for high-risk HPV types. 41.6% of samples were ASCUS, 8.33% were LGSIL and 20.3% were HPV positive. HPV 16 was detected in 8.33% of samples, and 54.16% of samples contained more than one HPV type, with maximum of five types observed in one LGSIL sample. A separate set of five samples, which were positive for the five high-risk HPV types, was analysed for E6/E7 mRNA expression using the PreTect HPV-Proofer, IVD Diagnostic kit. 40% of positive-samples expressed E6/E7 mRNA.

Conclusion: Our results suggest that the HPV E6/E7 mRNA assay can be a sensitive and specific tool for the screening and investigation of cervical cancer. Furthermore, it may provide useful information regarding the necessity for early cervical cancer screenings.

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O.P. 17

POLYCYSTIC OVARY SYNDROME AS A RISK FACTOR FOR PREMATURE OVARIAN INSUFFICIENCY : CONTROVERSIAL DATA

C. Pagkaki, A. Kontogewrgi, E. Fitsakis, E. Kouvidis, E. Ziogos, A. Makrigiannakis

University Hospital of Heraklion, Department of Obstetrics and Gynecology

Accredited Training Centre for Obstetrics & Gynecology by

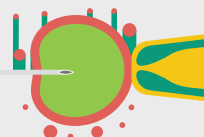
the European Board College of Obstetrics and Gynecology (EBCOG)

Text: Results of controversial studies between age of menopause and pcos are presented, possible correlation between pcos and premature ovarian insufficiency as well as suggested common mechanisms between the two syndromes

Objective: The objective is to examine if women with polycystic ovary syndrome have a higher probability of premature ovarian failure in their subsequent life and to suggest a possible common mechanism between the two syndromes based on the preexisting studies.

Methods: Literature review.

Patients: All the studies included white race women Interventions :We analyzed the results of published studies of the last eight years which correlated the age of menopause and the occurrence of PCOS. We search the literature for possible common mechanisms , as immune dysregulations and and common mutations between POI and PCOS Main outcome measures : There is one nationwide population-based study (Pan ML et al) that reveals prior PCOS is a significant and independent risk factor for development of POI. Contrariwise according to older studies and reviews the reproductive lifespan of PCOS women extends on average 2 years beyond that of normo-ovulatory women. Ovarian autoantibodies as possible common mechanism between PCOS and POI cannot be confirmed, as the presence of autoantibodies in PCOs is controversial between different studies and population ,due to the heterogeneity of the syndrome, variety of ovarian antigens as well as antibody tests leading to conflicting results. A possible common mechanism is the different response to progesterone between the women with PCOS and POI compared to the healthy population ,regarding its non- genomic actions. A swedish study suggests that reduced levels of progesterone receptor membrane component 1 (PRMC 1) in peripheral leukocytes are associated with perturbed ovulatory function, both in PCOS and POI.



Result: Polycystic ovary syndrome and premature ovarian insufficiency in the subsequent life could be related. A possible mechanism could include actions mediated by non genomic progesterone receptors as PGR1, which was observed to be reduced in both women with PCOS and POI.

Conclusions: Further studies must be carried out to ensure PCOS as a risk factor for primary ovarian insufficiency, as well as to clarify the mechanism of their connection.

O.P. 18

VULVAR ANGIOMYOFIBROBLASTOMA. A RARE CLINICAL AND SURGICAL TUMOR

C. Goudeli, E. Kouvidis, S. Patramani, F. Makrigiannakis, C. Pagkaki A. Makrigiannakis

University Hospital of Heraklion, Obstetrics-Gynecology, Iraklio- Crete, Greece

Accredited Training Centre for Obstetrics & Gynecology by

the European Board College of Obstetrics and Gynecology (EBCOG)

Aims: Angiomyofibroblastoma (AMF) is a benign tumor of the superficial soft-tissue, deriving from the mesenchymal cells of the subepithelial myxoid stromal area. We herein report a case of a 50-year-old woman surgically treated for a vaginal painless mass.

Method: A 50-year-old postmenopausal woman presented to the gynecology department due to mass-enlargement in the right part of the vulva, mainly occurring when standing. On clinical examination the lesion arise from the middle third to the right posterior vaginal wall. Her laboratory data were normal. Three years ago she was treated for a mass in left labia majora concerning a sebaceous cyst.

Results: The lesion was excised en block. The surgical specimen was firm with no areas of hemorrhage, necrosis or cystic transformation and measured 8X6X2,5cm. Microscopically, the mass had typical findings of AMF, such as hypo and hypercellular areas with thin-walled blood vessels. On immunohistochemistry, stromal cells were positive for desmin, myogenin, smooth muscle actin (SMA), S-100 and estrogen and progesterone receptors. The patient was released the day after with no post-operative problems.

Conclusion: AMF is a rare soft-tissue neoplasm of the vulva, vagina, scrotum, the inguinal area and the spermatic cord in males. It is usually described in women of reproductive age (46 years) as a painless mass causing dyspareunia and pressure. The differential diagnosis includes hernia, leiomyoma, aggressive angiomyxoma, cellular angiofibroma, bartholin gland cyst, lipoma. AMF has low recurrence potential and very rarely it can be transformed into sarcoma. The treatment is total local excision with or without embolization of its main artery.

O.P. 19

PEMPHIGUS VULGARIS IN PREGNANCY. A CASE REPORT

I. Kokolakis, D. Koutroulakis, D. Koumaki, S. Kruger, K. Krasagakis, A. Makrigiannakis

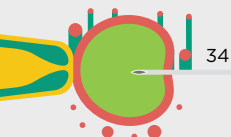
University Hospital of Heraklion, Department of Obstetrics and Gynecology

Accredited Training Centre for Obstetrics & Gynecology by

the European Board College of Obstetrics and Gynecology (EBCOG)

Aim: Pemphigus vulgaris (PV) is an autoimmune, bullous, mucocutaneous and potentially life-threatening disease. The occurrence of PV during pregnancy is exceedingly rare. We report a case of a 33-year-old woman who was firstly diagnosed with PV during pregnancy.

Material & Methods: At 22 weeks gestation the patient presented with widespread blistering dermatitis in the abdomen and associated burning and pruritus. A skin biopsy revealed suprabasal acantholysis, and direct immunofluorescence showed diffuse intercellular IgG in the epidermidis and basal intercellular C3, which confirmed the diagnosis of PV. In addition, anti-desmoglein I, III antibodies were positive. Treatment of high-doses systemic corticosteroids was instituted to control the disease after discussions with the patient about possible adverse effects to the fetus.



Results: PV may be associated with an adverse outcome, such as fetal growth restriction and preterm births. In our case 6 weeks after treatment, there was remission of the disease with no presence of new clinical-skin manifestations. The pregnancy is still in progress with no adverse outcomes.

Conclusion: The outcome of pregnancies complicated by pemhigus is generally good, but achieving good outcomes likely depends on the collaborative efforts of the obstetrician and dermatologist. Current data suggest increased rate of perinatal mortality. Pregnancy may have an uneventful course, nevertheless, careful monitoring of the high risk mother and fetus is mandatory.

O.P. 20

NON-OPERATIVE MANAGEMENT OF SPLENIC PREGNANCY WITH SELECTIVE EMBOLISM AND METHOTREXATE

V. Mytaras, S. Patramani, I. Drakakis, D. Tsetis, M. Raisaki, A. Makrigrannakis, Th. Vrekoussis, F.Makrigrannakis

*University Hospital of Heraklion, Department of Obstetrics and Gynecology
 Accredited Training Centre for Obstetrics & Gynecology by
 the European Board College of Obstetrics and Gynecology (EBCOG)*

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.

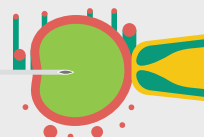
Objective: We report the first case of asymptomatic splenic pregnancy successfully treated non-operatively with selective embolization and adjuvant methotrexate administration intramuscularly.

Methods: 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 .

Discussion and Conclusions: 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. 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. 21

ASSEMENT OF UTERINE CAVITY BY HYSTEROSCOPY IN INFERTILE WOMEN WITH RECURRENT PREGNANCY LOSS AND RECURRENT IVF FAILURES (RIF).

M. Nikolaou, D. Kosta, G. Andreadakis, K. Ntzelepis, T. Katasos

Department of Obstetrics & Gynecology, General Hospital of Agios Nikolaos, Agios Nikolaos, Crete, Greece

Accredited Training Centre for Obstetrics & Gynecology by

the European Board College of Obstetrics and Gynecology (EBCOG)

Background-Aim: Intrauterine pathologies are present in 25-50% of infertile patients. Structural abnormalities of the uterine endometrial cavity affect reproduction outcomes because they interfere with implantation or cause spontaneous abortions. The goal of this retrospective study was to evaluate the diagnostic validity of diagnostic hysteroscopy in the detection of uterine cavity pathologies in infertile patients with recurrent implantation failure (RIF) or recurrent pregnancy loss.

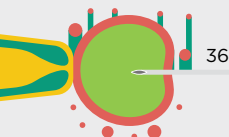
Material & Methods: This retrospective study was performed from November 2012 to July 2018. A total of 28 consecutive patients who were diagnosed with failed *in vitro* fertilization (IVF), intrauterine insemination (IUI) or recurrent pregnancy losses (RPL) were underwent diagnostic hysteroscopy. Most of the procedures were performed under IV sedation and normal saline (0.9%) was applied as the distention medium.

Results: The patients' ages ranged from 24 to 42 years (median was 34 years). In 17 patients (60.7%), a hysteroscopy did not find any abnormality of the uterine cavity. In 11 patients (39.2%) there were one or more abnormal hysteroscopic findings. The abnormal hysteroscopic findings in 11 patients in the majority were due to endometrial adhesions and scarring (10.7%), uterine septum (7.14%), arcuate uterus (3.57%), chronic endometritis (10.7%) and endometrial polyps ((7.14%). The pregnancy rate was significantly higher in patients who were treated by a hysteroscopy for a detected uterine abnormality. There were no complications recorded during or after the procedures.

Conclusion: Diagnostic hysteroscopy should be considered as an essential workup method prior to any further IVF cycles are considered in patients with a history of RIF, due to high prevalence of any predefined intrauterine pathologies.

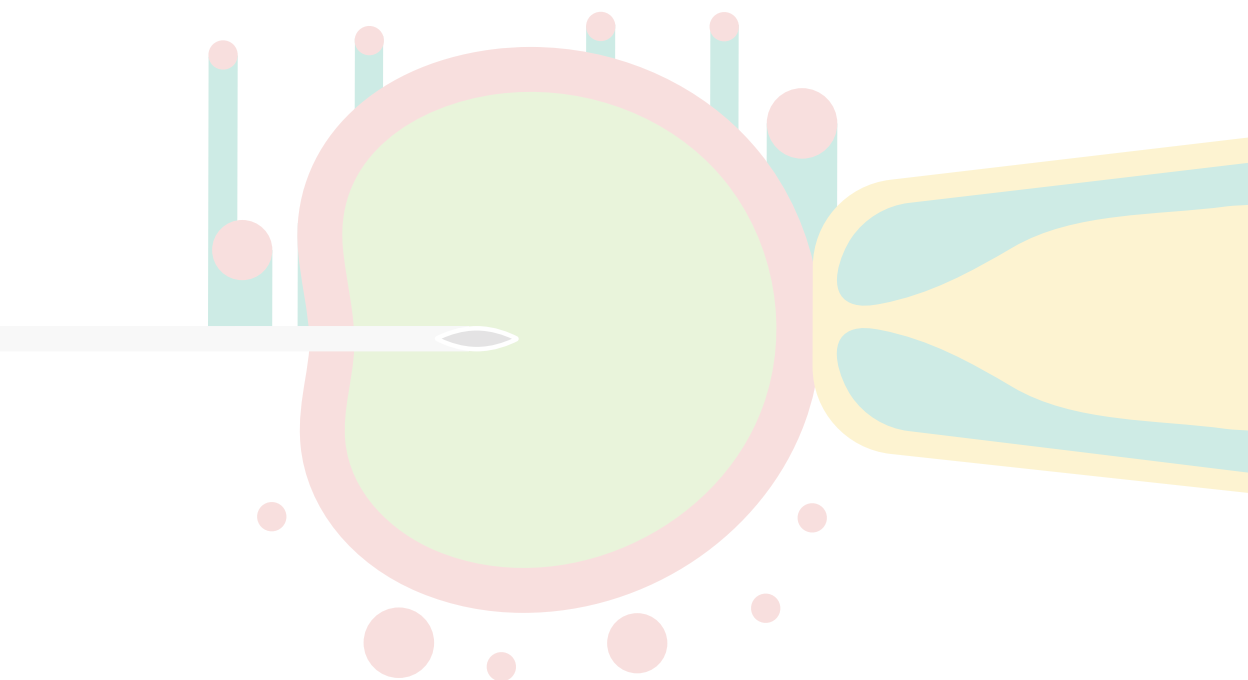
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ABSTRACT BOOK

Invited Speakers' Abstracts



MSRM
XV Annual Meeting
of the Mediterranean Society for Reproductive Medicine

HOT TOPIC I: "TUBAL SURGERY - EXTRAUTERINE PREGNANCY"**HyCoSy & HyFoSy: First Line Imaging in Tubal Infertility****S. Mousourakis, MD, PhD, DMRD, FRCR, CCST***Clinical Radiologist, Women's Imaging Specialist*

Purpose: to review the role of hysterosalpingo-contrast-sonography (HyCoSy) and its variant hysterosalpingo-foam-sonography (HyFoSy) in tubal infertility, and to discuss issues of technique and diagnostic performance, indications and side effects of these methods.

Tubal pathology is a frequent cause of infertility, usually due to ascending pelvic inflammatory disease from sexually transmitted infections. Tubal patency evaluation is essential in the diagnostic work-up of infertility.

Laparoscopy with chromopertubation is the "gold standard" of assessment of tubal patency. Laparoscopy is invasive and costly, requires anaesthesia and postoperative recovery, and may cause morbidity due to visceral damage and intra-abdominal bleeding.

Radiographic hysterosalpingography is the traditional method of tubal patency assessment. However, it gives no ovarian or adnexal information and provides inadequate imaging of the uterine cavity. Women may experience bleeding, pelvic pain or vasovagal reactions during or after the procedure. Hysterosalpingography exposes the patient to ionizing radiation and allergenic iodinated contrast media.

In hysterosalpingo-contrast-sonography (HyCoSy), and its newer variant, hysterosalpingo-foam-sonography (HyFoSy), three techniques are combined: transvaginal ultrasound, sonohysterography and sonosalpingography.

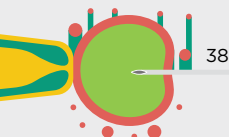
Transvaginal ultrasound is used for baseline imaging. The uterus is evaluated to determine the appearance and structure of the endometrium, myometrium and junctional zone, and to assess for congenital or acquired abnormalities (müllerian duct anomalies, fibroids, polyps, adenomyosis). The adnexa are examined with grayscale and Doppler imaging, looking for evidence of polycystic ovaries, ovarian and adnexal masses, or signs of tubal disease. The pouch of Douglas is evaluated for masses, signs of endometriosis, or excessive free fluid. The pelvis is examined for adhesions by pushing on the uterus and ovaries to assess organ mobility.

Sonohysterography is used for 2D and 3D imaging of the uterine cavity, as uterine cavity abnormalities are common in subfertile women. Sonohysterography involves placing a catheter through the external cervical os and instilling saline. The anechoic fluid distends the cavity by pushing the echogenic walls of the endometrium apart, giving hysteroscopic quality images of the uterine lining. Hysteroscopy, the main alternative to sonohysterography, is more invasive, requires local anaesthetic or sedation and does not allow the assessment of the myometrium or the adnexa. Sonohysterography should be avoided in women with an active pelvic infection. Performing the procedure between menstrual cycle days 6 and 11 helps to ensure the absence of pregnancy and facilitates maximum uterine cavity visibility with a thin, proliferative phase endometrium.

Indications for sonohysterography include the evaluation of abnormal uterine bleeding; uterine pathology such as submucous leiomyomas, polyps, and adhesions; transvaginal ultrasound findings needing clarification; congenital uterine anomalies; infertility; and recurrent pregnancy loss.

Systematic reviews have shown that sonohysterography is practically as sensitive and specific as hysteroscopy in the detection of intrauterine abnormalities (sensitivity: 90%, specificity: 95%, approximately). Sonohysterography can be used as a screening tool in the assessment of subfertile women, reducing greatly the need for hysteroscopy, with the added benefit of identifying extrauterine pathology.

Sonosalpingography is the technique of assessing tubal patency by infusing in the uterine cavity a sonographic contrast medium under mild pressure. The contrast agent outlines the lumen of the fallopian tubes, producing a hyperechoic appearance in real time. The simplest contrast medium is saline mixed with air, that is, a simple suspension of air bubbles. Image quality with air bubbles is crude, with areas of acoustic shadowing. The passage of air can be painful, leading to vasovagal reactions.



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Pharmaceutical grade ultrasound contrast media have a more stable hyperechoic appearance, making their movement easier to visualize through the fallopian tubes, and do not produce obscuring acoustic shadows. These contrast media, in effect gas microbubbles, show a substantial harmonic response at low acoustic pressure making them clearer and visible for longer. The shell material affects the microbubble's mechanical elasticity. The more elastic the material, the more acoustic pressure the microbubble can withstand without bursting. This increases time available for imaging. Microbubble shells can be composed of albumin, galactose, lipids, or polymers. In the second generation of ultrasound contrast agents, the air in the bubble has given its place to higher molecular weight gases resulting in more stable bubbles. SonoVue, the main representative of second-generation agents in Europe, is characterized by a microbubble structure consisting of sulfur hexafluoride gas stabilized by a phospholipid monolayer shell. It has been clinically tested for hysterosalpingo-contrast-sonography.

Limited availability and the high cost of echogenic contrast media has led to the introduction of a foamy gel (ExEm) as an alternative ultrasound contrast medium. ExEm foam gel contains glycerol, hydroxyethyl cellulose and purified water. This alternate form of sonosalpingography was first described in 2011, and termed hysterosalpingo-foam sonography (HyFoSy).

Several prospective and retrospective studies support HyCoSy as a reliable and reproducible screening procedure for subfertility. According to meta-analyses, the overall HyCoSy detection of occlusion and patency approaches 100% and 85%, respectively. Concordance for patency between the HyCoSy and comparative tests is quoted as 86% for laparoscopy and 84% for hysterosalpingography. Technical difficulties in HyCoSy are commoner in obese patients, in the presence of large fibroids, when multiple gas-containing bowel loops are present near the fallopian tubes, or if the ovaries are located beyond the reach of the ultrasound beam. Pitfalls of HyCoSy include: observed echogenic flow in one segment of the tube without confirmation of distal flow over the adjacent ovary (distal occlusion overlooked) and conversely, false positive results for occlusion secondary to tubal spasm. The fallopian tube cannot be seen completely in a single scanning plane due to its tortuosity. Visualization of the entire tube requires multiplanar scanning by an experienced practitioner who can quickly manipulate the transvaginal probe to visualize the different anatomical parts of the tubes. A learning curve of a few hundred procedures is necessary to optimize technique.

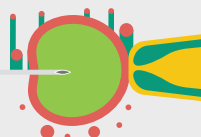
HyCoSy and HyFoSy are extremely well-suited as screening tests in the initial imaging of subfertility, allowing the consecutive evaluation of ovarian reserve and morphology, uterine cavity contour and myometrial structure, and tubal anatomy and patency.

3D scan and endoscopy: the complementary tools for tubal infertility

V. Tanos, MD, PhD

University of Nicosia, Medical School, Professor in Obstetrics and Gynaecology Team Leader ObGyn MD6 and Aretaeio Hospital Nicosia

The diagnosis of female infertility and primary care management should include 2D US. Meticulous TVS will provide information regarding endometrial-cavitary as well as myometrial pathologies and exclude or suspect congenital uterine anomalies. In combination with Colour doppler sub-endometrial and myometrial diffused adenomyosis can be suspected. Hence 2D US offers the 1st line management of infertility patients and screening for patients that will need further examination. The next investigation should include 3D abdominal and trans vaginal sonography whereas firm diagnosis can be made on type and dimensions of the congenital uterine abnormalities, the existence of adenomyosis and its exact location and the diagnosis of intracavitary lesions. Hystero contrast sonography with NS or foam usually will confirm or exclude intracavitary lesions like adhesions or small fundal indentations, placental remnants,



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polyps or adhesions. Micro lesions, endometritis like strawberry endometrium, micro endometriosis polypoidosis will be diagnosed and treated by hysteroscopy in an outpatient setting. Intraoperative US scanning is essential during hysteroscopic lysis of adhesions and myomectomy.

Tubal recanalisation after sterilization**A. Watrelot***Hôpital Natercia, Lyon- FRANCE*

Even if indication for sterilization are carefully discussed some women will regret their decision. Statistically demand of recanalization occurs after the death of one of the child, divorce or the death of male partner.

Ability to recanalize the tubes depends on the method chosen for sterilization:

-The use of Essure (where it is not possible to restore tubal permeability) has made the tubal recanalization less and less feasible. But the Essure system (this having been retired from the market in 2017, we may expect to see the number of indications to grow up again

-because now the main system of tubal sterilization is the tubal clipping through laparoscopy.

Since the clips create very little damage, tubal recanalization is of very good prognosis

-tubal cauterization destroys a bigger length of the tube and therefore the prognosis of recanalization is not as good as clips

-when sometimes partial distal salpingectomy has been performed, then the only option is IVF

If a patient regrets sterilization, it seems logical to propose the tubal recanalization whenever it is possible. 3 methods are possible: by microsurgery through minilaparotomy, laparoscopy or with the help of robot.

The best results are obtained by microsurgery or robotic surgery with a post-operative tubal permeability of 90%

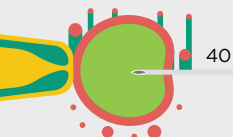
Laparoscopic tubal repair gives only 70% of permeability

Pregnancy rate depends on the age and ovarian reserve of the patients who are frequently over 40.

However, if the tubal repair is technically possible it should be systematically proposed since the results are at least as good as those obtained by IVF and the balance benefit/cost is in favour of surgery.

Best option for ectopic pregnancy: to operate or not?**V. Tanos, MD, PhD***University of Nicosia, Medical School, Professor in Obstetrics and Gynaecology Team Leader ObGyn MD6 and Aretaeio Hospital Nicosia*

Ectopic pregnancy is a life-threatening condition. However, early firm diagnosis by TVU today is feasible especially using 3D TVU. When the patient is haemodynamically stable and pregnancy sac is small and beta hCG is low then Methotrexate treatment should be the first line treatment. When interstitial pregnancy is diagnosed that laparoscopic surgery should be performed by experienced surgeon. Methotrexate treatment might be considered in special cases especially as an adjuvant treatment. Cervical pregnancy (CP) is one of the rarest types of ectopic pregnancies. Life-threatening hemorrhage due to CP may lead to hysterectomy and fertility loss. Prior uterine interventions such as curettage, cesarean section, and fertility treatments are well known risk factors for CP. Frequent presenting symptoms are vaginal spotting and low pelvic pain. Our case series and review of the literature demonstrated that operative hysteroscopy can be used as a sole treatment in early, less than 8-week CPs with safety.



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The diagnostic precision of hysteroscopy on implantation location facilitates the direct detachment of the CP using both hydro-dissection and 5Fr instruments, while reassuring hemostasis with 5Fr bipolar energy probes and/or resectoscope. The injection of vasoconstrictors into the healthy tissues adjacent to the CP is imperative and reduces the risk of bleeding during hysteroscopic evacuation. Hysteroscopic removal of CP can be used after failure of methotrexate treatment or in combination with uterine artery embolization (UAE). UAE seems to be an attractive treatment option especially in advanced gestational age and active bleeding cases.

A new chapter of tubal pathology: the subtle tubal lesions and their impact on infertility Subtle Tubal Lesions

A. Watrelot

Centre de Recherche et d'Etude de la Stérilité (CRES), Hôpital NATECIA_Lyon-France

According to the literature between 10 to 30% of infertile patients are classified as "unexplained".

The proportion is therefore very different from a work to another one

In fact it depends of the infertile work up performed before declaring an infertility as unexplained

A lot of authors consider that the infertility is unexplained if all standard test being normal such as Spermogram, hormonal profile and Hysterosalpingography(HSG) the couple doesn't conceive after 2 years. These couples are generally referred to ART

However it has been demonstrated that the number of unexplained infertility may be reduced if further explorations are performed leading to be able to discover some abnormalities and therefore to treat the patients accordingly.

Concerning the ability of the tubes , very often only HSG is practised, and we know the poor value of a normal HSG to detect tubal pathology.

We have also demonstrated that only endoscopy is able to have a proper evaluation of the genital tract and among endoscopy we have described fertiloscopy after the description by Gordts on transvaginal hydrolaparoscopy.

Fertiloscopy is able to show tubal abnormalities even subtle like ampullary sacculation, fimbrial agglutinations, non connective adhesions and abnormal tubal mucosa.

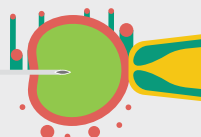
We are therefore able to classify these subtle tubal abnormalities according to their site: serous (adhesions) muscular (sacculation) or mucous (intra- ampullary adhesions for example)

In two different works we have studied the impact of these abnormalities.

The first one consisted to practice systematically a microsalingoscopy in so called unexplained infertility. Out of 1292 cases we have found 28,4% of mucosal abnormalities. We have directly referred these patients to IVF considering that an abnormal tubal mucos was not suitable to propose Intra uterine Insemination

The second work studied retrospectively 341 patients where subtle tubal lesions were found in 67 cases. Infertility history was quite long (2_13 years, range 3 years). When treated we obtained 34 (50,7%) pregnancies in the 6 following months.

The impact of these lesions seems to have been underestimated and we believe that we should look systematically at such abnormalities in order to propose directly the best therapeutic option and to decrease the number of unexplained infertility which is always a very distressful diagnostic for infertile patients.



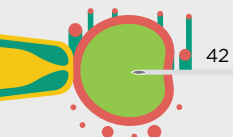
HOT TOPIC I: "TUBAL SURGERY - EXTRAUTERINE PREGNANCY"**Role of hysteroscopy in diagnosis and treatment of tubal pathology****T. Motrenko Simic***Human Reproduction Center, Budva, Montenegro*

Hysteroscopy is golden standard for evaluation uterine cavity. During procedures, both tubal ostia should be visualized, and very often fluid flow could be seen thru open ostia, or fluid with tissue particles or air bubbles spinning movement without any flow. In case of post-inflammation damage sometimes ostia could not be visualized at all, blocked with adhesive tissue. It could be useful in case of hydrosalpinx providing information does communication with uterine cavity exist or not. Performing ultrasonography before office hysteroscopy and after intervention, presence of fluid in coul-de sac, especially in amount over 6 ml, a part of visualization of fluid flow thru ostia is diagnostic procedure for tubal patency too. Many studies confirmed high accuracy of results comparing with laparoscopy performed after hysteroscopy. There is also new method with injecting highly concentrated methylene blue (10%) very near tubal ostia, previously reducing liquid pressure in uterine cavity, called hysteroscopic chromotubation, where could be seen methylene blue passage to tubes, one than another, since color do not mix so immediately with fluid. Accuracy was confirmed or not with later laparoscopy, with result sensitivity 85%, specificity 60%, positive predictive value 91%, negative predictive value 46%. In case of communicating hydrosalpinx, before IVF there is need to occlude connection between tube filled with fluid and uterine cavity to increase IVF success, reduced by 50% by hydrosalpinx presence. There is possibility to perform hysteroscopy needle electrocoagulation to tubal ostia, successful in 90%. Some studies report in case of unilateral hydrosalpinx and unilateral occlusion spontaneous pregnancy rate during following 6 months in 26% of cases, what is lower that after laparoscopic tubal ligation (50%). Still there is acceptable success rate of occlusion, 93% versus 96% after laparoscopic intervention. There is also possibility for hysteroscopic placement of tubal device called Essure, used for years especially in cases where laparoscopy could not be performed (frozen pelvis, other contraindication for laparoscopy), or because waiting for intervention was too long or health care insurance do not cover such intervention. Device was approved for human use with purpose to provide permanent sterilization in EU 2001, in USA 2002. Starting form 1998 it was many attempts, mainly in small studies to prove efficacy in tubal occlusion (very high, a part of laparoscopic tubal occlusion with monopolar electrocoagulation)and later IVF, with conflicting results. Depending of center performing study, results of IVF measured by clinical or ongoing pregnancy rate was similar or slightly reduced. Lately, RCT performed during 5 years period by Dreyer K and systematic review and meta-analysis performed by Xu B, proven that laparoscopy is superior to Essure placement, measured by clinical pregnancy rate, life birth rate and implantation rate. Still, there is place for hysteroscopic Essure usage for patients where laparoscopy is contraindicated. Hysteroscopy as diagnostic and therapeutic procedure still is important and unavoidable in tubal pathology diagnosis and treatment, even place in algorithm of infertility treatment and diagnosis is not adequately established.

What to do in case of hydrosalpinx? Prognostic factors and evaluation scores for hydrosalpinges. When to operate?**A. 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)



HOT TOPIC I: "TUBAL SURGERY - EXTRAUTERINE PREGNANCY"

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 chosen.

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.

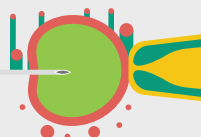
HOT TOPIC II: "MSRM DIPLOMA IN CLINICAL ASSISTED REPRODUCTION PART I"

Ovulation, fertilization, implantation

A. Makriannakis MD, PhD

Professor Ob/Gyn, *University of Crete*

Maternal age, in the developed world countries, has been steadily increasing over the years and is known to be the main cause of reduced reproduction success and a major risk factor for abnormal newborn development. The age-related reproductive decline in mammals is mainly attributed to the significant increase in oocyte chromosome segregation abnormalities. Recent studies, using animal models, have pinpointed that maternal age may be related with severe placentation defects and abnormal decidualization responses by the uterine stroma. Endometrium's decidualization process, its embryo receptivity and its role in embryo development is modulated by its environment. Changes in epithelial and stromal endometrium cell function, as well as changes in their gene and protein expression regulate the uterine environment and its characteristics. In our study, epithelial and stromal endometrium cell proliferation was investigated in relation to women's age. Endometrial biopsies from women undergoing hysterectomies were obtained, with informed consent. Tissues were cut, digested and filtered in order to separate the different cell populations - as described in previously published protocols. Epithelial and stromal endometrium cells were then cultured and either used in proliferation assays or collected for mRNA extraction in order to analyse gene expression using Real-time PCR. The expression of genes related to the decidualization process, cell proliferation and receptivity of the endometrium (BMP-2, Hoxa10, Hoxa11, E-Cadherin, STAT3) were associated with woman's age. The description of mechanisms and associated molecules that can affect the characteristics of the aging endometrium can aid to the understanding of the causes of reduced human fertility.



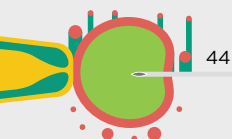
HOT TOPIC II:**"MSRM DIPLOMA IN CLINICAL ASSISTED REPRODUCTION PART I"****Ultrasound monitoring and oocyte retrieval****T. Motrenko Simic**

When ovarian stimulation starts, it is essential to monitor ovarian response and follicular growth in order to adjust gonadotropin dosage and determine time when follicles reach proper size for stop injection. Usually, we perform ultrasound monitoring 6-7 days after stimulation start and record size and number of follicles growing, adjusting gonadotropin dosage if it is needed. Patients are scheduled to be seen every other day until follicles reach proper size for triggering ovulation. This size differ for variety of protocols, but it is accepted for long one to be 20 mm, and for antagonist protocol when 3 leading follicles reach size 17-18 mm. But we have to have in mind there is small proportion of patients reacting differently from majority, and need more stimulation and even bigger size of follicles in order to get mature cells. Those patients are very often one coming with good antral follicle reserve and small number of oocytes retrieved in previous IVF cycle. If there was no previous IVF attempt, unfortunately there is no way to know this in advance. Also it is important to check does patient received properly stop injection, or receive at all, especially in case of first IVF attempt, because if it is not case we will not obtain oocytes at all, or very few oocytes in case of lower bHCG concentration. This could be avoided by asking patients to give blood sample for bHCG measuring in lab next morning after stop injection, so in case of not receiving, we will see almost unmeasurable bHCG concentration. Analyzing cases of so called empty follicles syndrome, 95% of those patients didn't received properly stop injection or got is in a wrong way so bHCG concentrations were very low. Still you can rescue cycles by repeating stop injection and rescheduling pick up, 34 to 36 hours after.

To prepare equipment properly we have to take care about sterility having in mind the needle will be in used to enter abdominal cavity and one of complication of procedure could be infection and tube-ovarian abscess. Probe is covered by sterile glow or better with sterilized cover designed in different size depending of operators preference and can cover probe and part of probe cable too. Needle guide could be reusable or disposable, even in case of other cost is much higher. There is variety of aspiration needles at market and choice depend of operator preferences. Still, it is important to choose needle with good visibility under ultrasound, rigid enough to follow line of aspiration without bending, and tubing system made out of high quality plastic, to avoid curling and stopping fluid to flow in case of needle rotation. Before we start with follicles aspiration it is recommended to wash needle with media, what will prepare aspiration system for oocytes and check aspiration pump before we start. Aspiration pump pressure should be around 120 up to 140 mm Hg, avoiding to high pressure to distort oocytes. Also, tubes for collecting follicular fluid should be kept in warm holder adjust of 37°C degree, since it is known cooling of oocytes can cause permanent genetic damage and increase aneuploidy, harming whole process and further success.

After preparing all and checking equipment we can start procedure. What we will choose for vagina washing depend of availability and our preference, from saline solution to some nontoxic disinfectant.

If this is possible probe should be placed to reach as much as we can with one puncture for ovary, what is sometimes difficult in case of higher number of oocytes or ovaries out of usual position. Technique for aspiration differs, some authors claim that rotating of needle will provide more oocyte, some other do not see the difference. But it is important to keep needle the middle of follicles in order to obtain all fluid inside; otherwise collapsed follicles walls will obstruct fluid flow and aspiration. Keep in mind probe direction and reach other follicles by moving forward and backward needle, holding firm the probe and do change of direction only when needle is on the proximal edge of ovary, but without rotation, since tip of needle could be invisible and lost on screen, causing damage to surrounding tissue or blood vessels or even organs. One of complication a part of infection is bleeding. Usually some small amount of bleeding came from fornixes, and could be stopped by simple pressure by gaze hold in instruments. But in case of bigger bleeding not stopping after pressure, even few stiches are needed in rare cases. Or



HOT TOPIC II:

“MSRM DIPLOMA IN CLINICAL ASSISTED REPRODUCTION PART I”

vaginal tamponade can be performed with close follow up of patients. A part of dominant follicles it is wise to aspirate even smaller ones knowing there is small chance that cell will be picked up, but for sure this will reduce ovarian size.

When we aspirate all follicles needle should be washed with media - we have to aspirate at least several medium milliliters to collect cells kept in aspiration system.

For beginners it is wise to start with ultrasound guided cyst aspiration just to become familiar with trans-vaginal puncturing and all tips and tricks related to this relatively simple procedure.

Dysbiosis and Microbiota in Infertility

T. Gürgan, Prof., Dr.

Bahçeşehir University, Faculty of Medicine, Department of Obstetrics and Gynecology

It is now known the female reproductive tract that once thought to be sterile is not sterile and has its own microbiota. Bacterial vaginosis disrupts the dominance of the Lactobacilli (doderlien rods) and increases the spectrum of bacteria in the vagina (*Gardnerella*, *Mycoplasma*, *Provetalla*). Thus, resulting in tendencies in various gynaecological infections such as Chlamydia, *Neisseria gonorrhoea*, *Trichomonas*, HPV, and herpes simplex type-2. Furthermore, the lactobacilli in the vagina produce hydrogen peroxide that serves as a virucide in defence against viruses such as HIV. Subclinical endometritis is found in 27% of women who has Chlamydia and 26% of women who has vaginal gonorrhoea. It is also possible that like disruptions in the vaginal microbiome, the disruptions in the uterine microbiome could result in infertility and/or pregnancy complications. These complications include early/late pregnancy losses, preterm birth, and endometritis following giving birth. There are several reports indicating that the follicular fluid content shows differences depending on the cause of infertility (PCO, endometriosis). Thus, if it were accepted that the disrupted vaginal, uterine, and follicular fluid microbiota has an effect on infertility, it would be logical to seek possible treatment options. Such an example for a possible treatment would be to use prophylactic antibiotics prior to IVF cycle to reduce the bacterial colonization in the upper genital tract to increase the pregnancy rates. However, up to date, this treatment method was found to be contradictory. More studies are needed to understand the microbiota of the female reproductive tract and its effect on infertility, and to develop treatment methods to improve it.

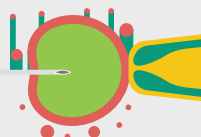
Key words: Infertility, microbiota, endometrial microbiome, vaginal dysbiosis.

Cryopreservation

B. Kovačič

Department of Reproductive Medicine and Gynecological Endocrinology, University Medical Centre Maribor, Slovenia

Cryopreservation of human gametes and embryos is an important and widely used method in most embryology laboratories. The cryopreservation protocols routinely used in IVF are simple and readily undertaken in commercially available equipment and cryopreservation media. However, an understanding of the basic principles of cryobiology is desirable to ensure that the methodology is correctly and successfully applied in order to minimise cell damage during the processes of freezing and thawing or processes of vitrification and warming. Cells can be stored at low temperatures such as -196°C and not above -150°C for unlimited time; the real challenge is their survival after returning to physiological conditions. One of the main issues in achieving the goal is the intracellular freeze that has to be overcome to increase sur-



**HOT TOPIC II:
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vival. To improve the outcome different protocols have been developed with the aim of reducing intracellular ice crystal formation. To do so, it is necessary to reach a sufficient dehydration thanks to specific molecules called cryoprotectant agents (CPAs) that can be differently mixed in order to maximize the outcome. These compounds can be divided into two groups according to their properties:

1. Permeating agents such as glycerol, dimethyl sulfoxide (DMSO), ethylene glycol (EG), and (1,2) propanediol (PROH). They all have a low molecular weight and can penetrate the lipid bilayer of the cell but slower than water.

2. Nonpermeating agents such as sugars and other macromolecules (ficoll, raffinose, as well as proteins and lipoproteins). They have a high molecular weight so they remain in the extracellular solution.

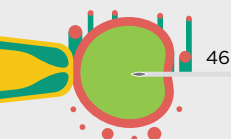
The basic task of the CPAs is to reduce possible damages due to ice crystal formation inside the cell.

Human gametes, embryos of various developmental stages and gonadal tissue can all be successfully cryopreserved, but for each of them a specific cryopreservation protocol is recommended.

The classical cryopreservation protocol is slow cooling method. It has been used for decades for cryopreservation of embryos and zygotes, and also for oocytes but with limited success. During this cryopreservation method the cells are very dehydrated by cryoprotectants and surrounded by concentrated salts. The cryoprotectants reduce possible damages caused by this osmotic milieu. They also decrease the likelihood of intracellular ice crystal formation. Afterward, the cells are cooled down to subzero temperatures slowly (around $-2^{\circ}\text{C}/\text{min}$) to avoid possible shock. Once the sample temperature has been lowered to -6 to -8°C (just below the equilibrium freezing point of the mixture), ice nucleation is induced by touching the straws or cryoampoules with precooled forceps. This procedure, known as seeding, allows the conversion of extracellular water into ice. After seeding, ice spreads throughout the entire solution but ice crystals do not enter the cell because of the marginally higher osmolarity (lower freezing point) of their intracellular environment. Following the seeding, the concentration of the solutes in the non-frozen fraction gradually increases as water is incorporated into the extracellular ice crystals. The increasing concentration in the solutes generates an osmotic gradient across the cell membrane, which draws more water out causing the cell to dehydrate. By lowering very slowly the temperature, nearly all of the water can be removed from the cell without ice crystal formation and, at the same time, damages caused by the extracellular solute concentration can be minimized. At this point the samples can be plunged directly in liquid nitrogen.

Classical slow freezing method are used also for cryopreservation of semen, testicular and also ovarian tissue. However, many cryobanks practice very simplified sperm freezing. Semen samples are mixed with cryoprotectants and exposed to liquid nitrogen vapours. After such simplified method of cooling, the straws are plunged in liquid nitrogen.

The vitrification is a method that was developed as the last one. It is superior for cryopreservation of large volume cells like oocytes and zygotes and also blastocysts which contain a large amount of liquid. This method is nowadays used also for cryopreservation of early cleavage stage embryos and thus one protocol can be used for all stages from oocytes to blastocysts. The principal goal of vitrification is to eliminate ice crystal formation entirely in the whole solution containing the embryos and oocytes. To achieve this ice-free glass-like solidification of solutions, which may also be defined as an extremely increased viscosity, high cryoprotectant concentrations and/or very high cooling rates are required. To decrease the potential osmotic and toxic damage caused by cryoprotectants, recent vitrification methods have focused on increasing the cooling and warming rates. Most successful vitrification methods are based on use of extremely small volumes of solution containing the specimens and direct contact between this solution and liquid nitrogen. The survival rate of blastocysts after vitrification and warming is more than 90% and clinical results very comparable to the outcome of transfers of fresh blastocysts. Cryopreservation of human gametes and embryos is recommended in different situations. Sperm banking can be used for storage of sperm donor semen and for fertility preservation of oncological patients before surgery, radio- or chemotherapy. During last years, the practice of single embryo transfer was



HOT TOPIC II: "MSRM DIPLOMA IN CLINICAL ASSISTED REPRODUCTION PART I"

a greater demand for reliable cryostorage of surplus embryos. Successful cryopreservation of oocytes opened new challenges in preservation of fertility in oncological patients and also in fertility preservation for non-medical reasons (social freezing). The only method with still high level of limitations is the cryopreservation of ovarian tissue where the conventional slow freezing is the most often used method.

Multichoice questions:

The long-term storage of human gametes and embryos requires the temperature of at least:

- 80°C
- 100°C
- 120°C
- 150°C**
- 196°C

The best survival of oocytes and blastocysts after cryopreservation is achieved by using:

- Slow freezing and fast thawing
- Vitrification and ultrarapid warming**
- Vitrification and slow warming
- Two step freezing and two step thawing
- Computer controlled cooling machine

Cryopreservation in liquid nitrogen is recommended for storage of:

- Donor semen until testing for viruses is not completed**
- Metaphase I oocytes for oocyte donation
- Surplus embryos from an IVF cycle**
- All embryos from an IVF cycle to prevent ovarian hyperstimulation syndrome**
- Immature oocytes from PCOS patients to prevent ovarian hyperstimulation syndrome

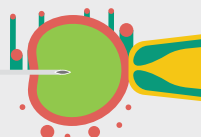
SESSION I: "CONTROVERSIES IN IVF"

Do we have any proof that boosting mitochondrial function in oocytes increases success?

T. Ebner

Kepler University, MedCampus IV, Linz, Austria

Mitochondria are essential cell organelles present in eukariotic cells mostly recognized for their role in generating cellular energy via OXPHO. Oocytes with normal mitochondria showing sufficient energy production are likely to be better suited for energy dependent processes such as meiosis and follicular establishment. On the other hand, dysfunctional mitochondria in oocytes/embryos could cause developmental problems in aged women and women with diminished ovarian reserve. In extreme, it can be associated with chromosomal segregation errors. In order to prevent these unwanted scenarios several methods, auto- and heterologous ones, have been reported which could rescue mitochondrial deficits. Although these approaches may work in some patients, to date, the idea that oocyte quality can be improved by cytoplasmic transfer and/or supplementation with mitochondria of somatic cell or germ line origin is rather not supported by literature.



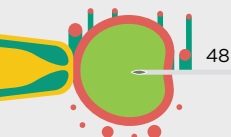
SESSION II: "FERTILITY PRESERVATION"**Update of fertility preservation results****P.N. Barri MD, PhD; F. Martínez MD, PhD; M. Devesa MD, PhD***Service of Reproductive Medicine, Dexeus Mujer, Hospital Universitario Dexeus, Barcelona*

Several oncological and non-oncological diseases may affect current or future fertility, either caused by the disease itself or the gonadotoxic treatment, and need an adequate FP approach. Women wishing to postpone maternity and transgender individuals before starting hormone therapy or undergoing surgery to remove/alter their reproductive organs should also be counselled accordingly.

Embryo and oocyte cryopreservation are first-line FP methods in post-pubertal women. Metaphase II oocyte cryopreservation (vitrification) is the preferred option. Cumulative evidence of restoration of ovarian function and spontaneous pregnancies after ART following orthotopic transplantation of cryopreserved ovarian tissue supports its future consideration as an open clinical application.

Semen cryopreservation is the only established method for FP in men. Testicular tissue cryopreservation should be recommended in prepubertal boys even though fertility restoration strategies by autotransplantation of cryopreserved testicular tissue have not yet been tested for safe clinical use in humans. The establishment of international registries on the short- and long-term outcomes of FP techniques is strongly recommended.

Concerns on the welfare of future offspring are not a reason to deny cancer patients access to assisted reproduction. Programmes offering storage of gametes, embryos or gonadal tissue should request clear instructions on what to do in case of patient's death, unavailability, nonpayment of storage fees and other contingency. The use of these biological materials by patients' partners will require specific informed consents clarifying the possible posthumous use of this material.



HOT TOPIC III:**«EMBRYOLOGY: BLASTOCYST BIOPSY: FROM THEORY TO PRACTICE»****New insights in embryology****R. Laura***Clinica Valle Giulia, GENERA centers for reproductive medicine, Rome, Italy*

IVF is among the fastest developing fields of medicine. Thanks to the pioneering work of Steptoe and Edwards and the courage of their first patients, nowadays thousands of infertile couples worldwide might benefit from assisted reproduction technologies. An intensive research activity in this field keeps modifying the present and shaping the future approaches and strategies.

The introduction of cryo-preservation represented a game-changer in IVF. Even if slow-freezing led to substantial improvements, vitrification is a real milestone, which allowed embryologists worldwide to boost oocyte/embryo cryo-survival rates. The optimization and the widespread application of cryopreservation in IVF largely increased also clinical possibilities including: i) the systematic application of an elective single-embryo-transfer policy; ii) the possibility to perform blastocyst biopsy and complex time-consuming genetic testing (PGT); iii) the application of cycle segmentation and freeze-all policy; iv) and the possibility to perform fertility preservation via egg banking for women wishing to postpone their desire of motherhood for either medical (e.g. cancer, endometriosis) or social issues.

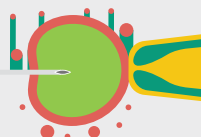
Several invasive and non-invasive strategies have also recently been proposed to improve embryo selection and encourage SET also in advanced maternal age (AMA) patients, thereby decreasing the risk for multiple pregnancies and their related obstetrical and perinatal consequences. The goal of embryo selection is indeed to recognize the most competent embryo(s) within a cohort produced by a couple during IVF, namely the one(s) with the highest chance of resulting in the birth of a healthy child.

Recently, time-lapse microscopy and embryo culture converged into the creation of undisturbed incubators. Such technology enhanced the conventional morphological assessments by involving the detection of several dynamic phenomena and criteria that could be useful to select/deselect the embryo(s) to transfer. Nevertheless, to date, it mainly represents an ideal incubation system rather than a tool to conduct embryo selection.

The most promising data to predict embryo implantation potential derived from the advances in PGT for aneuploidy. This strategy, that combines blastocyst culture, trophectoderm biopsy and vitrification needs a high-standard laboratory and highly-trained embryologists and even though has an incredible potential, is still very expensive and not accessible to all.

Many scientists focused their research upon the biology of human preimplantation embryos and the definition of the blastocyst-endometrial dialogue, aiming at unveiling its dynamics and some putative biomarkers of competence via '-omic' approaches (genomics, transcriptomics, proteomics etc.) applied to the investigation of non-invasive sources of oocyte/embryonic biological material (cumulus cells', follicular fluids', spent culture media, etc). Interesting perspectives may indeed derive from ground-breaking studies conducted in this field, especially through multidisciplinary approaches (e.g. stem cell research, microfluidics, automation).

The success of IVF must be grounded on cumulative-live-birth-rate per intention-to-treat and, via encompassing gynecological, embryological, psychological, genetic and social aspects, envision a personalized treatment for each couple. The future in IVF is yet to come with unpredictable avant-gardes.



HOT TOPIC III:**«EMBRYOLOGY: BLASTOCYST BIOPSY: FROM THEORY TO PRACTICE»****Genetics In IVF****D. Cimadomo, Dr, MSc, PhD***Molecular biologist. Scientific Coordinator of the G.EN.E.R.A. centers for reproductive medicine (Rome, Naples, Marostica and Umbertide, Italy)*

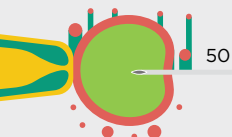
The genetic risks in human reproduction are imputable to either conditions present in the parental genotype or conditions occurring *de novo* in the embryos. The former include for instance single gene disorders, mitochondrial diseases as well as structural chromosomal rearrangements, while the latter are the direct result of chromosomal missegregation (i.e. aneuploidies) caused by errors occurring during gametogenesis (i.e. meiotic ones) and/or preimplantation development post-fertilization (i.e. mitotic ones). Preimplantation genetic testing (PGT) has been introduced in IVF to prevent the consequences of such conditions.

PGT-M and PGT-SR aim at the identification in the embryos of mutations causative of monogenic diseases or structural rearrangements, respectively. Their clinical value and efficiency to this end has been already clearly established, and still represent solid technologies nowadays.

PGT-A instead aims at the definition of aneuploid and euploid embryos in a cohort produced from a couple during an IVF cycle. Aneuploidies in the embryos are indeed the main cause of implantation failure, miscarriage and abnormal pregnancies in women mainly due to the concurrent reduction of their ovarian reserve and increase in the risk of meiotic errors as the woman (and her oocytes) ages. The main limiting factor to the application of PGT-A is the need to efficiently conduct blastocyst culture and vitrification; however, when trophectoderm biopsy and comprehensive chromosome testing were efficiently conducted, PGT-A showed several evidences of higher efficiency with respect to standard IVF (higher implantation rate per transfer, possibility to perform single embryo transfer and limit the risk for multiple pregnancies, lower miscarriage rate). Future studies would need to bring about evidences from randomized controlled trials conducted on a per intention to treat basis (i.e. definition of the efficacy, which needs to be similar between PGT-A and IVF), investigating time to pregnancy and cost-effectiveness. To this regard, the indications defined to suggest PGT-A are advanced maternal age, recurrent implantation failure and recurrent pregnancy loss. Severe male factor instead, even if associated with a reduced embryo developmental competence to blastocyst, is not causative of a reduced reproductive competence; therefore, evidences are missing to consider it as an indication to PGT-A *per se*.

Chromosomal mosaicism (i.e. the presence of cells in the same embryo characterized by different chromosomal constitutions due to a post-zygotic missegregation error) represents a diagnostic hazard only when both euploid and aneuploid cells are present. Such condition has been estimated to be as low as 7% when analyzing whole disaggregated blastocysts donated to Research, but might be largely over-estimated (ca.20%) when analyzing a single biopsy. The latter situation is imputable to biological and/or technical artifacts, intrinsic to the biopsy and its molecular analysis, which need to be acknowledged and possibly limited. Future non-selection studies are required to define the real clinical meaning of transferring (or not transferring) a blastocyst defined "mosaic" after comprehensive chromosome testing conducted on a trophectoderm biopsy.

Across the years from the first theorization of PGT in the 90s, several biopsy methods have been suggested and implemented in IVF. Blastocyst biopsy in day5-7 currently represents the main strategy: no impact on embryo reproductive competence, low risk for inconclusive diagnoses (ca.2.5%), no impact on embryo post-warming behavior, high standardization across several practitioners are some of its advantages reported to date. Indeed, its application in Europe in 2016 has even outnumbered blastomere biopsy approach according to the most recent data of the ESHRE PGD Consortium data (Barcelona 2018). In the future, minimally- (i.e. blastocentesis) or even non-invasive (i.e. culture media analysis) methods might find an application in the clinical practice of an IVF cycle, which would revolutionize the way we currently think of PGT and of its application. However, these avant-gardes still need extensive



HOT TOPIC III:**«EMBRYOLOGY: BLASTOCYST BIOPSY: FROM THEORY TO PRACTICE»**

validation and fine-tuning to overcome the consistent risks for amplification failure, DNA contamination and lack of reproducibility among different laboratories. The future might be bright in this field, but requires a multidisciplinary and collaborative approach between embryologists, geneticists and gynecologists.

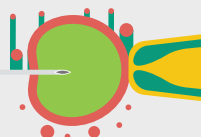
Embryo morphology assessment**T. Ebner***Kepler University, MedCampus IV, Linz, Austria*

It has been suggested (Alpha and ESHRE, 2011) that the current expected observation for embryo development is 4 cells on day 2 and 8 cells on day 3, depending on the time elapsed post insemination on average. Embryos that have cleaved more slowly than the expected rate may have a reduced implantation potential, and embryos that have cleaved faster than the expected rate are potentially abnormal and have a reduced implantation potential. This, however, has been postulated without taking numerous morphological parameters at cleavage stage (e.g., fragmentation, fragmentation pattern, number and size of blastomeres, nuclear status, cytoplasmic pitting, tetrafoliate shape, compaction) into consideration. In fact, many of these parameters have been reported to correlate with embryo implantation or blastocyst development, but few studies have focused on their interdependence. Time-lapse imaging has further shed some light on predictive morphological scoring of embryos. It is recommended to use all available (e.g., static morphology, time-lapse data, blastulation potential) when defining an embryo's implantation potential.

SESSION IV: "INCREASING ENDOMETRIAL RECEPTIVITY"**The embryo in RIF: genetic selection and strategies for improving its implantation potential****L. Gianaroli, M.C. Magli, A. Crippa***SISMER, Reproductive Medicine Unit, Bologna, Italy*

Embryo implantation is a crucial step of pregnancy establishment ensuing in a restricted time lapse, known as the window of implantation. For implantation to occur, the embryo and the uterus go through synchronous development and initiate a bidirectional crosstalk that leads to a clinical pregnancy. Several factors are involved in this complex process including embryo viability, the receptivity of the endometrium, and the maternal immune response. Defective arrangements in any of these compartments determine failure of implantation, a condition that, despite the optimization of treatment protocols and laboratory technologies, occurs repeatedly in patients presenting with repeated implantation failures (RIF). Several definitions have been proposed for RIF. In our center, we define RIF patients as those couples with a maternal age lower than 38 years having experienced at least three implantation failures after the transfer of high quality embryos.

Owing to the complexity of this condition, the category of RIF can be extremely heterogeneous and the management of these patients poses a major challenge to IVF professionals. An important role in the aetiology of RIF can be ascribed to gametes and embryos, and particularly to chromosomal abnormalities that represent the major cause of embryo wastage.



SESSION IV: "INCREASING ENDOMETRIAL RECEPTIVITY"

Some studies have documented an increased frequency, although at a modest degree, of chromosomal abnormalities in the oocytes from young RIF patients when compared to controls. The majority of our data come from FISH analysis on polar bodies. In a study involving 79 RIF cycles and 111 controls, 50% of first polar bodies were aneuploid in RIF vs. 44% in controls ($P < 0.05$). A similar trend was observed in 17 RIF cycles and 32 controls where both polar bodies were analyzed resulting in 44% and 58% aneuploidy rates respectively. When passing to array-CGH for 24-chromosome analysis, we observed the same tendency in a small series of treated cases (60% aneuploidy rate in 12 RIF cycles vs. 46% in 10 controls). It is well known that the contribution to embryo aneuploidy from the male gamete is generally modest. However, our FISH data for nine chromosomes on sperm samples from 331 young RIF couples showed that 18% of them have an incidence of aneuploidy significantly higher than the reference value ($P < 0.001$). Aneuploidy can arise during meiosis or after fertilization. The majority of chromosomal abnormalities arising at cleavage stages occur during the first three mitotic divisions, often leading to chromosomal mosaicism. Due to the implications of aneuploidy, preimplantation genetic testing for aneuploidy (PGT-A) has been proposed to improve the clinical outcome. This has been reported to be true especially if embryo biopsy is done at the blastocyst stage Greco et al., 2014, reported 68.3% clinical pregnancy rate in 43 young RIF patients after PGT-A vs. 21.2% in 33 RIF patients with similar indications, where embryo transfer was performed without PGT-A. According to our experience in young RIF patients, the clinical pregnancy rate increased from 32% when embryo biopsy was done at the cleavage stage to 50% after trophectoderm biopsy.

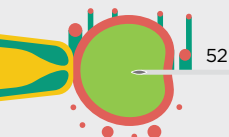
In conclusion, although only scarce data are available in the literature, we consider PGT-A a valuable strategy in the treatment of young RIF patients. This will only be true for those cases where a high incidence of chromosomally abnormal embryos is the preponderant cause of this unfortunate condition. Therefore, due to the heterogeneity of these patients' category, an accurate diagnosis of infertility will be the key element to overcome this infertility disorder.

**SYMPOSIUM MERCK SERONO
«INDIVIDUALIZATION AND PRECISION IN IVF»****Optimize FSH & LH in IVF protocols****K. Kostaras, MD, PhD, OB-GYN***Fertility specialist, Ivf unit ioLIFE-IIASO*

Both *folliculogenesis* and *proper oocyte maturation* are assisted by the synergistic action of FSH on GC's, via the FSHR, and by the action of LH on theca cells and GC's, via the LHCGR. This synergy is mediated via a balanced modulation of the steroidogenic cAMP/PKA-pathway on the one hand and the proliferative anti-apoptotic signals of ERK1/2-AKT pathway on the other hand.

Generally FSH is used as standard treatment while HCG or LH may be added to the regimen as well. HMG possesses LH-like activity due to the presence of LH and/or HCG molecules. However, LH trigger higher levels of ERK 1/2-AKT proliferative and anti-apoptotic signals than HCG which acts more via the cAMP/PKA steroidogenetic and pro-apoptotic activity in GC.

It is well known that the oocyte number predicts the LBR. There is a strong association between the number of oocytes retrieved and the cumulative LBR, if we transfer both fresh and frozen embryos during the same treatment cycle. The cumulative LBR increases as the number of oocytes retrieved increases.



SYMPOSIUM MERCK SERONO
«INDIVIDUALIZATION AND PRECISION IN IVF»

The patient could be classified as poor responder (1-3 oocytes), suboptimal responder (4-9 oocytes), normal (10-15 oocytes) or high responder (>15 oocytes).

The euploidy rate of embryos is independent from the number of blastocysts obtained but not from the age factor. More oocytes means more euploid blastocysts, more chances to transfer.

RCT's and metanalyses comparing oocyte yield with different gonadotropins demonstrate that the number of oocytes retrieved is higher with r-FSH vs. HMG, HP-HMG, uFSH.

In a RCT (MEGASET), on 2011, that compares HP-HMG and r-FSH in GnRH antagonist cycles with single embryo transfer, blastocyst, the ongoing pregnancy rates are similar but rFSH yields more oocytes. This means higher number of available blastocysts, in started cycle, that is more chance to transfer from frozen thawed embryos.

The role of LH during early follicular phase: LH induces androgen production in theca cells, increases FSHR in GC, possesses synergistic action with IGF1, increases the pre-antral and antral recruitment. During the mid follicular phase LH induces the expression of LHCGR in GC and sustains the FSH granulosa activities (via aromatase, growth factors etc.) contributing to the oocyte final maturation.

Which patient groups may need LH?

Patients with relative LH deficiency, as in cases of COS, in certain genetic conditions (e.g. resistance in gonadotrophins) and in the age group over 35 years old.

LH could be a corrective measure for relative LH deficiency by increasing the FSHR responsiveness, via the anti-apoptotic effect on GC's, via its steroidogenic action and via the upregulation of growth factors, acting synergistically with IGF1.

LH and HCG are not equivalent in vitro. HCG is steroidogenic and proapoptotic while, on the other hand, LH acts as an anti-apoptotic, differentiation-inducing and survival factor.

Experimental evidence suggests prolonged exposure to HCG is detrimental to endometrial receptivity. In a case control study with 4,719 patients (Bucler, Fischer Gyn.End.2011), treated with rFSH-rLH, HMG, rFSH-HMG, the LBR per started cycle is higher with rFSH-rLH. The effect is observed in both age groups, under and over 35 years old.

There are a lot of data about LH supplementation but they include different sub groups in the same group (high heterogeneity), so it is difficult to estimate which patients could benefit the most.

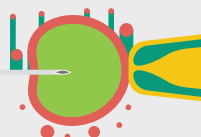
We may approach better the meta-analysis if we consider the efficacy of LH on specific sub groups of patients as in the recent review by C.Alviggi (Fert.Ster.v.109,n4, April 2018),

The addition of rLH is useful in the hypo-responders (with normal ovarian reserve) sub group, increasing significantly the FORT.

In women between 35-40 years old (normal ovarian reserve) rLH supplementation improves implantation rate compared with rFSH alone. Increase in implantation rate is associated with similar number of oocytes that means improved oocyte quality. LH given during COS acts on theca cells and in synergy with FSH on GC's in order to finalize the oocyte maturation.

Konstantinos Kostaras MD ,PhD
 OB-GYN. Fertility specialist
 Ivf unit ioLIFE-IIASO

GC=granulocyte cells
 LBRT= life birth rate
 FORT= follicular output ratio



SESSION V: "ENDOMETRIOSIS - ADENOMYOSIS"**Diagnosis of endometriosis: What is new?****K. Dafopoulos**

Professor of Obstetrics and Gynecology, Department of Obstetrics and Gynecology, Head of the ART Unit, University of Thessaly, Larissa, Greece

Endometriosis is a common disorder, affecting about 10% of women of reproductive age and up to 50% of women with pelvic pain and infertility. It is widely accepted that the gold standard for the diagnosis of endometriosis is the histological confirmation of lesions assessed by laparoscopy. However, there may be a delay of up to 9 years between symptom onset and definitive diagnosis of endometriosis, due to the need for laparoscopy for diagnosis, the variability of symptoms and the overlap in symptoms with other diseases. Although transvaginal ultrasound can identify deep nodules and ovarian endometriomas, it is not helpful in diagnosing superficial peritoneal endometriosis. Today, scientific research prioritizes the development of noninvasive diagnosis of endometriosis by using various biomarkers. This would hasten the diagnosis of endometriosis, decrease the need for surgery, and provide the means for non-invasive monitoring of the disease. Biomarkers for endometriosis have been investigated in peripheral blood and also in endometrial samples as a semi-invasive procedure. Based on the pathophysiology of endometriosis many biomarkers in peripheral blood including CA-125, cytokines, inflammatory proteins, markers of oxidative stress, immunity, autoimmunity, cell survival, adhesion, migration and pain pathways markers have been investigated. Between the endometrial biomarkers for endometriosis, the study of nerve fiber growth has shown promising results. Besides, "omics"-technology may discover potential biomarkers of endometriosis, while simultaneously providing new insights in the pathophysiology. Studies regarding protein or peptide fingerprints in peripheral blood and endometrium have shown promising results. Also, mRNA sequencing of endometrial samples revealed dysregulated genes in endometriosis. Recent studies have suggested that microRNAs, long non-coding RNAs and short inhibitory RNAs may influence endometriosis development, raising the possibility that such molecules may be included in new diagnostic tests. Finally, metabolomics has shown different metabolic profiles between endometriosis patients and controls. In conclusion, new diagnostic tools targeting at early identification of endometriosis will probably include a panel of biomarkers, which should be validated by properly designed studies.

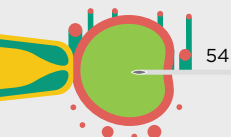
Endometrioma and IVF: Where is the evidence?**O. Sefrioui Pr, MD**

Anfa Fertility Center, Private center of reproductive medicine and fertility preservation, Casablanca, Morocco

Ovarian endometriomas are a common manifestation of endometriosis that can represent a more severe stage of the disease. There is much debate over the treatment of these cysts in infertile women, particularly before use of assisted reproductive technologies.

Evidence exists that supports surgical excision of ovarian endometriomas, as well as evidence that cautions against surgical intervention. Certain factors need to be examined closely before proceeding with surgery or continuing with expectant management.

Both endometrioma-related injury and surgery-mediated damage may be claimed to be involved and the relative importance of these two insults remains to be clarified. Convincing evidence has emerged showing that responsiveness to gonadotrophins after ovarian cystectomy is reduced. Conversely, the impact of surgery on pregnancy rates is unclear since no deleterious effect has been reported. Of relevance here is that surgery exposes women to risk related to a demanding procedure whereas risks associated with expectant management are mostly anecdotal or of doubtful clinical relevance. We rec-



SESSION V: "ENDOMETRIOSIS - ADENOMYOSIS"

commend proceeding directly to IVF to reduce time to pregnancy, to avoid potential surgical complications and to limit patient costs. Surgery should be envisaged only in presence of large cysts (balancing the threshold to operate with the cyst location within the ovary), or to treat concomitant pain symptoms which are refractory to medical treatments, or when malignancy cannot reliably be ruled out.

SESSION VI: "CONTROVERSIAL ISSUES"

Blastocyst versus cleaved embryo transfer: do we have enough evidence?

M. Aboulghar, M.D.

Professor, Faculty of Medicine, Cairo University, Cairo, Egypt, Clinical Director, The Egyptian IVF Center, Maadi, Cairo, Egypt

Improved laboratory standards and improved culture media made extended culture to blastocyst a reality. Extended culture was done to mimic natural physiology of blastocyst reaching the cavity days 5-6 and to ensure embryonic genome activations.

Randomized studies showed significantly higher pregnancy and delivery rates after blastocyst transfer. The objective is to transfer one blastocyst, thus preventing multiple pregnancy with all its complications and cost. However, recent Cochrane reviews showed that cumulative live birth rate per started cycle was not improved by blastocyst transfer.

Blastocyst transfer was associated with increased incidence of premature labour, higher perinatal mortality, higher risk of monozygotic twins, possibly due to genetic and epigenetic factors. There is also the possibility that no embryos will reach the blastocyst stage after extended culture.

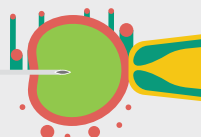
Blastocyst stage should be kept for patients with 4 or more excellent embryos at day three of the cycle.

In vitro maturation (IVM) – impact on embryos' and children's development

T. Strowitzki, Prof. Dr. Dr. h.c.

Introduction: In vitro maturation IVM of human oocytes prior to in vitro Fertilisation has been implemented in clinical practice in the last two decades. IVM is defined as oocyte collection from small follicles <10 mm without or with minimal hormonal stimulation and no controlled ovarian hyperstimulation followed by in vitro maturation of immature eggs for 24 hrs. and immediate fertilization of resulting MII oocytes. Main indications are patients with PCOS and a high oocyte yield and in particular a high risk for developing ovarian hyperstimulation syndrome. Although meanwhile widely used, data on developmental competence of the resulting embryos and children's development are still scarce. There is still consistent concern on lower embryonic competence, a higher malformation rate or altered epigenetic programming. Embryo development after IVM: Embryo development evaluated by time lapse imaging differs from embryos derived from mature MII oocytes. In a series of 23 IVM patients with PCOS compared to 16 PCOS patients with conventional stimulation IVM embryos reached tPNa faster and showed deceleration in all phases up to blastocyst stage. Albeit a lower number of good quality embryos the live birth rate was comparable (Rösner et al. 2017). Furthermore IVM does not increase the frequency of chromosomal abnormalities in human embryos compared to standard IVF (Zhang et al. 2010).

Children's development: In a prospective controlled single blind study we have analysed children's development up to 2 years compared to matched pairs after standard IVF and ICSI (Rösner et al. 2017). During pregnancy no differences at first and second trimester screening were found. Perinatal parameter



SESSION VI: "CONTROVERSIAL ISSUES"

showed also no difference. Comparable obstetrical and perinatal outcomes have been described in a series of other studies (Cha et al. 2005, Shu-Chi et al. 2006, Söderström-Anttila et al. 2006, Buckett et al. 2007, Fadini et al. 2014, Walls et al. 2015). Furthermore we couldn't detect any altered methylation patterns in chorionic villous and cord blood samplings compared to standard IVF/ICSI (Pliushch et al. 2015). Children's development up to 2 years has been addressed in several studies. Mental development was normal at 2 yrs. (standards of healthy Finnish children as control, Söderström-Anttila et al. 2006), also confirmed in another study (Shu-Chi et al. 2006). In our study cognitive performance at the age of two was analysed by Bayley II mental development index MDI. Mean MDIs were within normal range. Biometric parameters at the age of two showed also no difference to children conceived by IVF or ICSI.

Summary: IVM is a feasible, time saving, well priced and few side effects-including method for a well selected group of patients. No altered methylation patterns have been found. To our current knowledge children after IVM develop normally.

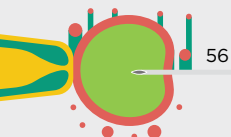
SYMPOSIUM DELLA SOCIETA ITALIANA DELLA RIPRODUZIONE UMANA (SIRU)**Consecutives Ejaculates In Ivf. Possible Improvements****C. Manna***Biofertility IVF and Infertility Center, Rome, Italy*

Keywords: sperm morphology, sperm motility, sperm DNA fragmentation, ART, semen analysis.

This study demonstrates the improvement motility, morphology, and DNA fragmentation in a series of normospermic and oligospermic men after a short abstinence period up to 60 minutes before and after swim-up.

Semen analyses and swim-up preparations of consecutive semen samples were carried out in 30 normospermic and 35 subfertile subjects enrolled in our IVF program. The second sample showed a higher mean normal morphology (20,4% versus 22,4%, $p < 0,01$) and reduced spermatozoa DNA fragmentation (14,8% versus 13,6%, $p < 0,01$) in normospermic subjects, while a higher mean progressive motility and normal morphology (16,9% versus 27,5%, $P < 0.001$ and 13% versus 15,6, $P < 0.0001$, respectively) resulted in subfertile subjects. In normospermic swim-up preparation showed only a reduction of DNA fragmentation (12,7% versus 11,2%, $p < 0.05$). In pathologic patients the improvement of semen parameters with swim-up preparation between the first and the second regarded normal morphology (24,1% versus 31%, $p < 0,01$) and spermatozoa DNA fragmentation (21,6% versus 16,7, $p < 0,001$). Our data show that swim-up can select better spermatozoa in consecutive sperm samples specially of subfertile patients.

Semen sample and swim-up preparations of consecutive samples collected within 60 minutes in both in normo- and specially oligozoospermic men might be usually carried out for IUI- IVF-ICSI procedures.



SYMPOSIUM DELLA SOCIETA ITALIANA DELLA RIPRODUZIONE UMANA (SIRU)**Should Hysteroscopy be performed in all patients before IVF?****P. Inaudi, L. Troia, S. Luisi***Obstetrics and Gynecology, Department of Molecular Medicine and of Development University of Siena, Siena, Italy*

The introduction of hysteroscopy in gynaecologic practice revolutionized the diagnosis and treatment of intrauterine disease. New technologies have made diagnostic and operative hysteroscopy much more efficient, cost effective, safe, and useful. Although the major indication for hysteroscopy is abnormal uterine bleeding, it is also widely used in cases of infertility and congenital anomalies (Bakour et al, 2006). The implantation failure during in vitro fertilization (IVF) has two main reasons: embryo quality and endometrial receptivity (Margalioth et al 2006). Implantation of the embryo is a complex process that involves anatomic, biochemical, immune and local factors. Intrauterine lesions are common in infertile women (40-50%) (Bosteels et al, 2013) and several studies suggest increased pregnancy rates after the hysteroscopic removal of endometrial polyps, submucous fibroids, uterine septa, or intrauterine adhesions. Hysteroscopy is actually considered as the gold standard for the diagnosis of intrauterine anomalies, offering the possibility to solve most of the diagnosed pathology in same act (Taylor et al, 2008). However in the medical literature, there is no adequate evidence concerning routine hysteroscopy before starting with an IVF cycle. The ESHRE guidelines recommends hysteroscopy only for the evaluation and treatment of suspicion of uterine pathology (Crosignani et al, 2000) and according to the ASRM (Practice committee 2012), hysteroscopy should be reserved for further evaluation and treatment of abnormalities defined by less invasive methods such as HSG and sonohysterography.

Actually, OH performed after repeated embryo implantation failure increases the chance of pregnancy in the subsequent IVF cycle, both in women with abnormal or normal hysteroscopic findings (Cenksoy et al, 2013, Carneiro 2014).

Lorusso et al. (2008) suggest that hysteroscopy as a routine infertility examination should be performed in all cases, owing to the elevated incidence of hysteroscopic pathological findings. Performing OH before IVF-embryo transfer, however, does not seem to add a value in improving pregnancy outcomes.

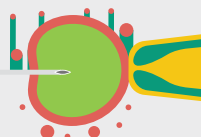
The safety and diagnostic value of hysteroscopy before IVF were examined also in 220 infertile women scheduled for ICSI. Abnormal findings were seen in hysteroscopy in 22.7% of the intervention group. The pregnancy rate in the intervention group (48.20%) was significantly higher than that in the control group after correction of endometrial cavity abnormalities (Alleyassin et al., 2016).

In 2014, Pundir et al. did a systematic review on using hysteroscopy before the first IVF cycles. They analyzed 6 randomized controlled studies, with a total of 3,179 cases, among which 1,277 did hysteroscopy before doing IVF and 1,902 cases started IVF without hysteroscopy. They concluded that clinical pregnancy and live birth rate improve in women who have hysteroscopy.

Karayalçin et al. (2012) enrolled 1258 patients attending an IVF clinic with normal hysteroscopic findings in an attempt to establish the impact of timing of office hysteroscopy before embryo transfer on pregnancy rate. The implantation, pregnancy, and clinical pregnancy rates were significantly improved when OH was performed 50 days or less before embryo transfer.

OH also allows to perform endometrial biopsies in infertile patients capable of detecting inflammatory/infectious processes that has been associated with poor reproductive outcomes in the context of ART. In cases of chronic endometritis (CE), the endometrial receptivity is reduced probably due to the hyperactivity of the immune system and to the altered secretion of various cytokines. Recent clinical studies showed that antibiotic treatment for CE may improve IVF outcome in patients with recurrent implantation failure. Notably, the resolution of CE should be confirmed with bacteriological examination, before proceeding with IVF (Vitagliano et al, 2018).

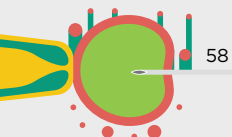
Our experience allows us to support the above reported indication, thus avoiding to highlight any uterine diseases only after the failures of one or more IVF cycles.



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Hysteroscopy may additionally improve endometrial receptivity and embryo implantation secondary to endometrial scratch injury (Nastri et al, 2015), but it is still unclear after how many failed ET attempts ESI may be beneficial (Vitagliano et al, 2018).

In conclusion, provide office hysteroscopy in all patients before starting IVF cycles, seems to be a reasonable option because this approach bring benefit to patients, providing not only diagnosis but also treatment for endocervical and intrauterine pathology. Hysteroscopy allows to perform, in patients without visible uterine diseases, endometrial biopsy able to detect abnormal endometrial patterns or infectious diseases, that may adversely affect the success of infertility treatment in absence of an adequate treatment.



SESSION VII: "CONTROVERSIAL ISSUES"

ART and long term outcome of the descendants

D. Loutradis, Prof.

Chairman 1st Department of OB/GYN Athens Medical School

Assisted reproduction technologies (ART), such as IVF and ICSI are widely used to solve human infertility. ART has provided great benefits for millions of couples who have struggled with infertility disorders. Since the birth of Louise Brown in 1978, there has been a tremendous growth in the use of ART. As the offspring of ART have become a substantial proportion of the population, the safety of ART has gained increasing attention. Concern has emerged that children conceived by ART might be exposed to greater health risks than naturally conceived (NC) children. Ovulation induction medications, in vitro culture of embryos, vitrification and the potential use of genetically and structurally abnormal sperm during ICSI are independent risk factors.

In this presentation we discuss the following subjects: Neonatal outcomes, Birth defects, Growth and gonadal development, Physical health, Neurological and neurodevelopmental outcomes. However, special focus is to concentrate our investigation to the proteomic, metabolomics profile of children born after ICSI compared with naturally conceived (NC) controls in search of cardiometabolic risk markers and epigenetic abnormalities.

Proteomics of Children Born After Intracytoplasmic Sperm Injection Reveal Indices of an Adverse Cardiometabolic Profile:

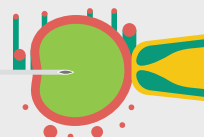
The ICSI group had shorter gestation, more cesarean sections, smaller birth weight/length, and advanced maternal age. No major differences were observed regarding biochemical markers. Proteomic analysis revealed 19 over- and three underexpressed proteins in ICSI. Most overexpressed proteins are implicated in acute-phase reaction, blood coagulation, complement pathway activation, and iron and lipid metabolism, suggesting a subclinical unfavorable cardiometabolic profile. This study applies proteomics in ICSI-conceived children, providing evidence for an early adverse cardiometabolic profile and supporting the necessity of their long-term monitoring.

Gender dimorphic increase in RBP-4 and NGAL in children born after IVF: an epigenetic phenomenon?

Children born after IVF had significantly higher RBP-4 ($P = 0.009$) and NGAL ($P = 0.028$) levels than controls. When divided by gender, RBP-4 remained higher in IVF girls ($P = 0.002$), whereas NGAL was higher in IVF boys ($P = 0.021$). Linear regression analysis had revealed that the differences are attributed to the IVF procedure per se. In our study, IVF children had significantly higher RBP-4 and NGAL levels than controls, suggesting early metabolic derangements that could be attributed to an epigenetic phenomenon. These results are in accordance with our earlier findings of higher blood pressure and triglycerides in IVF children than controls. Further prospective studies in IVF children will determine the natural course of their metabolic profile.

Plasma Metabolomic Profiling Suggests Early Indications for Predisposition to Latent Insulin Resistance in Children Conceived by ICSI.

Auxological and biochemical parameters of 42 6.862.1 yrs old ICSI-conceived and 42 age-matched controls were measured. Significant differences between the groups were determined using univariate and multivariate statistics, indicating low urea and low-grade inflammation markers (YKL-40, hsCRP) and high triiodothyronine (T3) in ICSI- children compared to controls. Moreover, plasma metabolomic analysis carried out for a subgroup of 10 ICSI- and 10 NC girls using Gas Chromatography-Mass Spectrometry (GC-MS) indicated clear differences between the two groups, characterized by 36 metabolites linked to obesity, insulin resistance and metabolic syndrome. Notably, the distinction between the two girl subgroups was accentuated when both their biochemical and metabolomic measurements were employed. The present study contributes a large auxological and biochemical dataset of a well-defined group of pre-pubertal ICSI-conceived subjects to the research of the ART effect to the offspring's health. Moreover, it is the first time that the relevant usefulness of metabolomics was investigated. The acquired results are consistent with early insulin resistance in ICSI-offspring,



SESSION VII: "CONTROVERSIAL ISSUES"

paving the way for further systematic investigations. These data support that metabolomics may unravel metabolic differences before they become clinically or biochemically evident, underlining its utility in the ART research.

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Altogether, ART is likely to cause some epigenetic changes in the offspring, which might be the molecular basis of complex traits and diseases. However, it is still unclear whether the small differences observed in several studies represent a real difference between ART-conceived and NC children. Larger studies with long-term follow-up are needed to fully answer these questions.

SESSION VIII: "PREECLAMPSIA"**Should we screen for preeclampsia? What for.****A. Antsaklis, Prof.**

Preeclampsia is a syndrome of new onset of hypertension and either proteinuria or end-organ dysfunction after 20 weeks of gestation.

The definition of preeclampsia as proposed by the International Society for the study of hypertension in pregnancy is: In previously normotensive women systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg at least 2 occasions in a row after 20 weeks of gestation and proteinuria ≥ 300 mg in 24 hours.

Preeclampsia (PE) is an important and leading cause of maternal and perinatal mortality and morbidity, is responsible for about 18% of maternal deaths and affects about 2-5% of pregnancies lead to over 100,000 maternal deaths worldwide each year and clinical manifestation can appear anytime from the second trimester to the first few weeks postpartum.

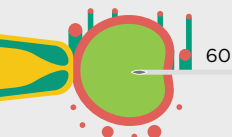
Is a disease of humans only, is the most common medical disorder, more common in primigravidas and elderly multipara and more common in black race and in winter.

Preeclampsia also is associated with an increased risk of poor fetal growth. The clinical findings can manifest as Maternal syndrome (Hypertension, proteinuria, with or without other multisystem abnormalities) and Fetal syndrome (fetal growth restriction, reduced amniotic fluid, abnormal oxygenation)

Maternal and perinatal outcome depend on Gestational age, time of disease onset, severity of the disease, quality of management and the presence or absence of pre-existing medical disorders.

The moderate risks criteria of development PE are: Nulliparity, obesity, family history of preeclampsia, age >35 years, socioeconomic characteristics and increased placental tissue.

The high risks criteria are: previous pregnancy with PE, multi fetal pregnancy, chronic hypertension Type 1 or 2 DM, renal disease and autoimmune disease.



SESSION VIII: "PREECLAMPSIA"

The pathogenesis of preeclampsia is incomplete understood and starts with an impaired remodeling of uterine spiral arteries, reduced placental perfusion, increased inflammation, increased production of anti-angiogenic factors and damage of the maternal endothelial cell and differs with various risk factors. The pathophysiological process occurring in two stages:

Stage 1: Reduced placental perfusion due to abnormal placentation.

Stage 2: Maternal systemic manifestations (inflammation, metabolic syndrome thrombotic responses)

Preeclampsia maybe caused by an imbalance of angiogenic factors and the combination of high serum levels of soluble fms like tyrosine kinase with the low levels of placental growth factor predict subsequent development of PE.

PE is not preventable but early diagnosis and appropriate management may prevent some dangerous complications.

First trimester screening represents a major advantage over a second trimester approach. Screening has to be simple, rapid, non-invasive, inexpensive, easy to perform and should not expose the patient to discomfort.

Maternal history with biophysical workers and biochemical markers are used for screening tests. Prophylactic treatments is likely to be more beneficial when started earlier in pregnancy.

Maternal characteristics like age, BMI, ethnicity, smoking status, chronic hypertension, DM, parity, previous PE, previous IVGR with the combination of biophysical parameters like mean arterial pressure and uterine artery Doppler and biophysics parameters like mom PAPP-A, free b-hcG, PIGF (reduced), sFet-1 (elevated), PPI3, ADAM 12, are parameter used for predicting PE early in pregnancies.

Studies agreed that a multi factorial algorithm is the most promising screening test for predicting of PE. A systematic review of screening tests for PE concluded that no single test is yet available to provide good diagnostic accuracy. Combined screening using several markers is more likely to provide the best prediction.

SESSION IIX: "ADOLESCENCE GYNECOLOGY"

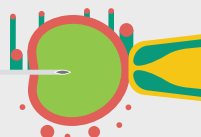
How to prevent and/or treat uterine bleeding problems

E. Deligeoroglou, MD, PhD

Full Professor of Obstetrics & Gynecology, Medical School, National and Kapodistrian University of Athens

Chairman in 2nd Department of Obstetrics & Gynecology, Medical School, National and Kapodistrian University of Athens, "Aretaieion" Hospital

Abnormal Uterine Bleeding (AUB) is a term, which describes a variety of symptoms, including heavy menstrual bleeding, intermenstrual bleeding and the co-existence of heavy and prolonged menstrual bleeding. The International Federation of Gynecology and Obstetrics (FIGO) propose a new classification system for the diagnosis of AUB in nulligravid women of reproductive age. Specifically, FIGO suggests the acronym PALM-COEIN, which stands for the following causes of AUB: Polyp, Adenomyosis, Leiomyoma, Malignancy and hyperplasia, Coagulopathy, Ovulatory dysfunction, Endometrial, Iatrogenic, and Not otherwise classified. In otherwise healthy adolescents, the most common cause of AUB is Dysfunctional Uterine Bleeding (DUB). More than 95% of DUB cases are due to anovulation. Although DUB remains a diagnosis of exclusion, other underlying pathologies such as bleeding disorders, pathologies of the reproductive tract, trauma, pregnancy, medication, as well as other endocrine disorders should be taken



SESSION IIX: "ADOLESCENCE GYNECOLOGY"

under consideration, before setting the diagnosis. Additionally, DUB can be subsumed in ovulatory dysfunction in the classification system of AUB.

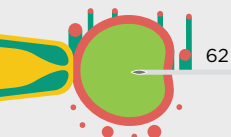
The list of diagnoses to be considered while approaching the problem of abnormal vaginal bleeding in reproductive-aged women is long but necessitates the careful examination and investigation of each patient. Some causes require immediate exclusion because failure to do so may result in significant morbidity and mortality. Pregnancy-related complications for instance, can present with any pattern of abnormal bleeding and among them ectopic pregnancy is one of the most serious conditions to be considered. Patients with pelvic inflammatory disease (PID) and endometritis frequently present with heavy or irregular bleeding or with vaginal bleeding combined with lower abdominal pain. The possibility of coagulopathy should be kept in mind, particularly in adolescents whose menstrual history is short and not yet well defined. The possibility of an underlying abnormality is high, if a woman has to be hospitalized and her hemoglobin is less than 10 g/dL.

Management of AUB is based on the underlying etiology and the severity of the bleeding. Primary goals are prevention of complications, such as anemia and reestablishment of regular cyclical bleeding. The management of AUB can in part be directed by the amount of flow, the degree of associated anemia, as well as patients' and family's compliance with different treatment choices. Patients' management falls into four major categories: (1) light to moderate flow and hemoglobin >12 g/dL, in which Non-Steroidal Anti-inflammatory Drugs are usually effective, (2) moderate flow with hemoglobin 10-12 g/dL and (3) heavy flow with hemoglobin 8-10 g/dL and hemodynamically stable in which oral contraceptive pills should be used and final (4) heavy flow and hemoglobin <7 g/dL and/or hemodynamically unstable, in which admission to hospital, blood transfusion and high dosages of oral contraceptive pills are required. Furthermore, a surgical treatment may be needed in case of contraindications to medical management, patient's lack of response to medical management, patient's clinical instability and persistent and severe bleeding. This, consist of, dilation and curettage (D&C), endometrial ablation, uterine artery embolization and finally hysterectomy, based on patient's desire for future fertility.

In conclusion, the etiologies of acute AUB should be classified based on the PALM-COEIN system. Medical management should be the initial treatment for most patients, if clinically appropriate, while, the need for surgical treatment is based on the clinical stability of the patient, the severity of bleeding, contraindications to medical management, the patient's lack of response to medical management, and the underlying medical condition of the patient. Finally, once the acute bleeding episode has been controlled, transitioning the patient to long-term maintenance therapy is recommended.

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