



MSRM

International Meeting

How to increase
success in IVF

25
SEPTEMBER 2015
27

HERAKLION
Atlantis Hotel
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**FINAL PROGRAMME &
BOOK OF ABSTRACTS**

MSRM

International Meeting



How to increase success in IVF

25-27 September 2015

Atlantis Hotel, Heraklion Crete

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ACKNOWLEDGEMENTS

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GREEK

Adonakis G.
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 Vrekoussis Th.
 Zikopoulos K.
 Zoumakis E.

Dear Colleagues and Friends,

On behalf of the Organizing Committee, I have the pleasure to welcome you all at the **International Meeting of the Mediterranean Society for Reproductive Medicine (MSRM)** which will be held in **Crete, Greece** from **25th** to the **27th September 2015**, at the **Aguila Atlantis Hotel in Heraklion, Crete**.

The theme of the Meeting is **“How to increase success in IVF”** and its main topics, will be:

- ANDROLOGY
- ENDOMETRIOSIS
- ENDOMETRIUM
- FERTILITY PRESERVATION
- HPV AND INFERTILITY
- HYSTEROSCOPY
- IMMUNOLOGY OF IMPLANTATION
- IMPLANTATION
- LAPAROSCOPY
- ORAL CONTRACEPTIVES
- OVARIAN STIMULATION
- P.O.F
- PCOS
- REPEATED IMPLANTATION FAILURE
- REPRODUCTIVE ENDOCRINOLOGY
- STEMM CELLS
- ULTRASOUND

Your participation will contribute to fulfill the expectations for a meeting of excellence and high scientific level in several fields of Reproductive Medicine and we invite all authors to submit abstracts related to the above topics.

As Heraklion is the capital of classical Crete, you will have the opportunity not only to attend a high-quality scientific meeting, but also to enjoy a late summer tour around the city with historical treasures, unique architecture and romantic atmosphere.

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



Professor Antonis Makrigiannakis
Meeting Chairman

14:00	REGISTRATION	
16:00-17:00	ORAL PRESENTATIONS <i>Chairmen: Adonakis G., Vrekoussis Th.</i>	
O.P.01	TRANSVAGINAL ULTRASOUND AND PELVIC ENDOMETRIOSIS Stratoudakis G, Patramani S, Tzitzikalakis C, Zouridis A, Daskalakis G. Department of Obstetrics & Gynecology of General Hospital of Chania, Kriti, Greece	
O.P.02	METHODS OF EMERGENCY CONTRACEPTION Stratoudakis G, Patramani S, Tzitzikalakis C, Zouridis A, Daskalakis G. Department of Obstetrics & Gynecology of General Hospital of Chania, Kriti, Greece	
O.P.03	SPONTANEOUS ABORTION AND RECURRENT MISCARRIAGE: A COMPARISON OF CYTOGENETIC DIAGNOSIS IN 198 CASES Kontodiou Maria ¹ , Siomou Eliza ¹ , Siahami Anthoula ¹ , Karambournioti Evangelia ² , Malathrakis Dimitrios ² , Papoulidis Ioannis ¹ , Manolakos Emmanouil ¹ ¹ Access To Genome (ATG) Labs, Athens - Thessaloniki ² Centre for Reproductive Medicine, Heraklion, Crete	
	Pre - Congress Course - CONTRACEPTION	
17:00-18:30	ROUND TABLE 1 "Contraception: What is good clinical practice?" <i>Chairmen: Makrigiannakis A., Limperis V.</i>	
	Adolescence. New Oral contraceptives and HPV infections Emergency contraception Contraception in adolescence Contraception in perimenopause	Creatsas G. Siristratidis C. Deligeoroglou E. Dafopoulos K.
18:30-19:00	COFFEE BREAK	
19:00-20:30	ROUND TABLE 2 "Combined Oral Contraceptives: Risks and Benefits" <i>Chairmen: Creatsas G., Stefos Th.</i>	
	Oral contraceptives and cancer risk Oral contraceptives and carbohydrate metabolism Oral contraceptives and cardiovascular risk Oral contraceptives and thrombosis risk	Daponte A. Mastorakos G. Kalanitaridou S. Drakakis P.
20:30-21:00	OPENING LECTURE <i>Chairman: Makrigiannakis A.</i> <i>Speaker: Sallam H.</i>	
	"Violence against women - what the gynaecologist should know"	
21.00-21.30	OPENING CEREMONY	
21.30	WELCOME RECEPTION	

08:00- 09:00

ORAL PRESENTATIONS

Chairmen: **Adonakis A., Vrekoussis T.**

O.P.04 THROMBOPHILIC AND FIBRINOLYTIC DEFECTS IN PCOS WOMEN WITH RECURRENT MISCARRIAGES

Evangelou Theoharis¹, Vartholomatos George², Karatzeni Irene¹, Gazos Ektoras¹, Kritikou Maria¹, Kokori Styliani³, Koutoulakis Ioannis¹, Navrozogou Iordanis¹, Vrekoussis Thomas¹, Kolaitis Nicolaos², Stefanos Theodor¹, Makrigiannakis Antonis⁴, Kalantaridou Sophia¹

¹Division of Reproductive Endocrinology, Department of Obstetrics and Gynecology, University Hospital of Ioannina, Ioannina, Greece

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³Blood Bank Department, Attikon Hospital, University of Athens Medical School, Athens, Greece

⁴Department of Obstetrics and Gynecology, University Hospital of Heraklion, University of Crete Medical School, Heraklion, Greece

O.P.05 OXIDATIVE STRESS UPREGULATES A-TOCOPHEROL TRANSFER PROTEIN IN HUMAN TROPHOBLAST TUMOR CELLS

E. Gazos¹, RP. Etzl², S. Heublein², I. Navrozoglou¹, Th. Evangelou¹, S. Kalantaridou¹, A. Makrigiannakis³, U. Jeschke², T. Stefanos¹, T. Vrekoussis¹

¹Department of Obstetrics and Gynecology, Medical School, University of Ioannina, Greece

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³Department of Obstetrics and Gynecology, Medical School, University of Crete, Greece

O.P.06 PROTECTIVE AND RISK FACTORS OF SUCCESSFUL IN-VITRO FERTILIZATION OUTCOME: PRELIMINARY RESULTS

Argyroula Kalaitzaki, Stella Mavrogiannaki, & Antonios Makrigiannakis

¹Social Work Department, School of Health and Welfare Services, TEI of Crete, Heraklion, Crete

²In vitro Fertilization Unit, General University Hospital of Heraklion, Heraklion, Crete

³School of Medicine, University of Crete, Heraklion, Crete

09:00-10:15

SESSION I

Chairmen: **Watrelot A., Zikopoulos K.**

- The dilemma to choose the FSH starting dose in IVF **Aboulghar M.**
- Improving live births rates in poor responders. Stimulation protocol strategies.
The role of hCG **Loutradis D.**
- How aggressive we need to be with luteal phase support.
Progesterone, Estrogen, GnRh agonists or hCG? **Kolibiannakis S.**

10:15-11:30

SESSION II

Chairmen: **Sallam H., Messinis I.**

- What is the optimal approach for endometriosis in ARTpatients? **Feki A.**
- What is the optimal approach for severe adhesions, should be treated before IVF? **Watrelot A.**
- What is the optimal approach for Repeated Implantation Failure patients? **Makrigiannakis A.**

11:30-12:00	COFFEE BREAK	
12:00-13:00	SATELLITE SYMPOSIUM FERRING "The evolution of ART: Where can we make a difference?" <i>Chairmen: Makrigiannakis A., Sfakianoudis K.</i>	<ul style="list-style-type: none"> •Biomarkers in the ART. Can they make the difference? Christoforidis N. •hCG/ LH debate: Which component can make the difference? Mantoudis E.
13:00-14:00	SATELLITE SYMPOSIUM MERCK SERONO "Clinical data for the role of LH in everyday practice in IVF" <i>Chairmen: Tartatzis V., Mastrominas M.</i>	<ul style="list-style-type: none"> •Clinical data for LH usage in IVF. Who, when & which Vlachos N. •The role of recombinant LH in IVF in daily clinical practice Tsakos E.
14:00-15:00	LUNCH BREAK	
15:00-16:30	SESSION III <i>Chairmen: De Sutter P., Creatas G.</i>	<ul style="list-style-type: none"> •What is the effect of Stress in Reproduction? Zoumakis E. •What is the optimal approach for ovulation induction in PCO patients? Messinis I. •The best options for the treatment of infertility in women with PCOS: A practical overview Tartatzis V. •Problems and complications during PCOS treatment of infertility Gurgan T.
16:30-17:45	SESSION IV <i>Chairmen: Veiga A., Mastrominas M.</i>	<ul style="list-style-type: none"> •Double embryo transfer (DET) is bound to improve outcomes? Lockwood G. •Day 3 or Day 5 for embryo transfer? Veiga A. •Should PGS be offered to all IVF patients? Rienzi L.
17:45-18:15	COFFEE BREAK	
18:15-18:45	MSD DEBATE "GnRH antagonist VS GnRH agonist protocol in IVF. Which are their advantages in ART today?" <i>Chairman: Bokal E.</i>	<ul style="list-style-type: none"> GnRH agonist protocol Sfakianoudis K. GnRH antagonist protocol Papanikolaou E.
18:45- 19:15	KEY NOTE LECTURE <i>Chairman: Loutradis D.</i>	<ul style="list-style-type: none"> What is the optimal approach for IUI versus intercourse or IVF? De Sutter P.

08:00-09:00

ORAL PRESENTATIONS

Chairmen: **Giakoumakis I., Vrekoussis T.**

O.P.07

PRODROMAL PRIMARY OVARIAN INSUFFICIENCY WITH INTERMITTENT OVARIAN FUNCTION IN A 19-YEAR-OLD WOMAN PRESENTING WITH SECONDARY AMENORRHEA

Gazos Ektoras¹, Dalkalitsis Alexandros¹, Vrekoussis Thomas¹, Vrachnis Nicolaos², Deska Eleutheria¹, Zikopoulos Konstantinos¹, Dalkalitsis Nicolaos¹, Kalantaridou Sophia¹
¹Division of Reproductive Endocrinology, Department of Obstetrics and Gynecology, University Hospital of Ioannina, Ioannina, Greece
²Second Department of Obstetrics and Gynecology, Aretaieion Hospital, University of Athens Medical School, Athens, Greece

O.P.08

THE ROLE OF DECIDUAL MACROPHAGES IN SPONTANEOUS ABORTION: UP-REGULATION OF FASL EXPRESSION

Th. Evangelou¹, S. Heublein², S. Guenther², I. Navrozoglou¹, E. Gazos¹, S. Kalantaridou¹, A. Makrigiannakis³, U. Jeschke², T. Stefanos¹, T. Vrekoussis¹
¹Department of Obstetrics and Gynecology, Medical School, University of Ioannina, Greece
²Departments of Obstetrics and Gynecology, Campus Innenstadt and Campus Grosshadern, Ludwig Maximilians Universitaet, Munich, Germany
³Department of Obstetrics and Gynecology, Medical School, University of Crete, Greece

O.P.09

ELEVATED CSF-1 EXPRESSION BY THE EUTOPIC ENDOMETRIUM OF WOMEN WITH ENDOMETRIOSIS: EVIDENCE OF CRH/UCN-MEDIATED CSF-1 UPREGULATION

A. Vergetaki¹, T. Vrekoussis², L. Sabatini³, E. A. Papakonstanti⁴, A. Makrigiannakis¹
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³Centre for Reproductive Medicine, St Bartholomew's Hospital, London, United Kingdom
⁴Department of Biochemistry, Medical School, University of Crete, Heraklion, Greece

09:00-10:30

SESSION V

Chairmen: **Gurgan T., Vrachnis N., Sifakis S.**

- Sonography in human Reproduction. New methods for evaluation of infertile patients and early pregnancy
- Reproducibility of Endometrium in ART patients
- 2D and 3D evaluation of the uterine cavity? Is it enough. The role of hysteroscopy?
- Complications of pregnancies resulting from assisted reproduction

**Radunovic N.
Vlaisavljevic V.**

**Motrenko T.
Sallam H.**

10:30-11:00

KEY NOTE LECTURE



Chairman: **Messinis I.**

- The role of sperm chromatine in couple infertility and its sensitivity to dietary manipulation

Dattilo M.

11:00 -11:30

COFFEE BREAK

11:30-13:00

SESSION VI

Chairmen: **Agorastos T., Drakakis P., Klentzeris L.**

- When is myomectomy is indicated in ART patients?
- What is the optimal approach for adenomyosis in ART patients?
- Fertility preservation: How to balance potential benefits versus risks
- HPV infection: Impact on infertility patients and possibility of prevention

**Tanos V.
Grimbizis G.
Rodolakis A.
Agorastos T.**

13.00-14.00

CLOSING REMARKS

Makrigiannakis A.

14.00-15.00

PUBLIC SESSION

Open Session for the public regarding Repeated Implantation Failure
Makrigiannakis A., Sallam H.

CALL FOR ABSTRACTS INFORMATION FOR AUTHORS

The Scientific Committee invites authors to submit abstracts related to the below mentioned topics and to be considered for inclusion in the Scientific Program as Oral or Poster Presentations.

Participants wishing to contribute to the Scientific Program of the Meeting are kindly requested to submit their abstracts before **August 14th, 2015** together with the registration form and the registration fee of at least one author (Presenting).

All abstracts must be submitted by e-mail: info@era.gr, and must be original and have not been published or presented at any previous conferences / meetings.

The Scientific Committee will endeavour to schedule abstracts according to authors' preferences but reserves the right to decide on the final form of presentation.

TOPICS

- ANDROLOGY
- ENDOMETRIOSIS
- ENDOMETRIUM
- FERTILITY PRESERVATION
- HPV AND INFERTILITY
- HYSTEROSCOPY
- IMMUNOLOGY OF IMPLANTATION
- IMPLANTATION
- LAPAROSCOPY
- ORAL CONTRACEPTIVES
- OVARIAN STIMULATION
- P.O.F
- PCOS
- REPEATED IMPLANTATION FAILURE
- REPRODUCTIVE ENDOCRINOLOGY
- STEMM CELLS
- ULTRASOUND

ABSTRACT FORMAT

1. Size: The abstract should not exceed **250 words**.
2. Style: We recommend structuring the abstract into paragraphs, like **Background, Aims, Methods, Results, Summary / Conclusions**. The abstract must be typed in **English in Times New Roman 11pt** and will be adjusted in size for printing.
3. Please enter your information as follows:
 - a) Title: The title must be in capitals and should not exceed 20 words.
 - b) Authors' names: The name of the Presenting Author should be mentioned first underlined. Separate multiple authors with commas.
 - c) Institution(s): Abbreviate if necessary; full postal addresses are not required.
 - d) Background: A short introduction is needed to the background of the study. Limit information to the essentials. If you are referring to published work please cite it.
 - e) Aim: Please mention the aim of the study.
 - f) Methods: Give enough details for the reader to understand what techniques were used; include details of statistical methods.
 - g) Results: Results must be stated. If the method should ordinarily produce numerical data, then numbers must be presented with appropriate statistical results.
 - h) Summary/Conclusions.
 - i) References (up to three): Surname(s), initials, title of paper, volume, pages, and year.



Crete, the island of king Minos in the southern part of the Aegean Sea, is full of natural beauties to explore and enjoy. Picturesque ports and sandy beaches with transparent waters will help you relax and at the same

time discover the continuing fascination and attraction of the island. The temperature of the sea in September is ideal for swimming and Cretan beaches have been awarded the European blue flag for clean waters and care for the environment.

VENUE

The Meeting will be held in Heraklion, Crete at Atlantis Hotel.

2, Igiass Street, Heraklion, 71 202 Crete, Greece

Tel: +30 2810 229 103 • Fax: +30 2810 226 265 • Web site: www.aquilahotels.com

DATES

The Meeting will be held on 25 - 27 September 2015.

KEY DATES

Deadline for **Abstract Submission:** **August 14th, 2015**

Full payment for **Reservations:** **September 1st, 2015**

SCIENTIFIC PROGRAM

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

CONTINUING MEDICAL EDUCATION

The Meeting has been accredited by the European Accreditation Council for Continuing Medical Education (EACMME-UEMS) with **13 CME-CPD** credits. Each participant should claim only those hours of credit that he/she actually spent in the educational activity. According to 81867/19.11.2012 EOF (National Organization for Medicines) each delegate must attend the 60% of total hours of the Scientific Programme and deliver to the Meeting Secretariat.

SCIENTIFIC PRESENTATIONS

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

SLIDE AND PC RECEPTION

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

CERTIFICATE OF ATTENDANCE

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

SECRETARIAT AND HOSPITALITY DESK

The Meeting Secretariat desk will be located nearby the Meeting Hall and will operate throughout the Meeting hours.

LANGUAGE

ENGLISH is the official language of the Meeting.

WEATHER AND DRESS

The weather in Crete during the month of September is pleasantly warm, ideal for sight-seeing and swimming, with temperatures ranging from 20°C to 25°C. For all outdoor evening events, sweater or jacket will be necessary.

LETTER OF INVITATION

Persons requiring an invitation letter in order to attend the Meeting may write to the Meeting Secretariat. 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 through 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 2 or 3 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 accepted.

TRADE EXHIBITION

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

REGISTRATION FEES

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

REGISTRATION (VAT INCLUDED)

General Participation € 246

The registration fees for participants cover:

- Access to the scientific sessions and exhibition
- Certificate of attendance
- Meeting material
- Coffee breaks and light lunch

ACCOMMODATION PACKAGE

For All Participants € 200

Rate includes: 2 nights accommodation bed & breakfast in single room, at the Aquila Atlantis Hotel

CANCELLATION AND PAYMENT CONDITIONS FOR REGISTRATION AND ACCOMMODATION PACKAGE

CANCELLATION CONDITIONS

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

- For cancellation of registration, received by **August 4th, 2015**, a refund of the total fee, less 25% as administration charge, will be made. After that date refunds for registration will not be possible.
- For cancellation of accommodation package, received by **August 18th, 2015**, a refund of the total fee, less 50% will be made.
- After that date refunds for accommodation package will not be possible.

PAYMENT CONDITIONS

- 50% of the accommodation package, payable to **ERA Ltd**, is required in order to confirm your Hotel Reservation
- Full payment for accommodation package should reach the Meeting Secretariat, not later than **September 1st, 2015**.

METHOD OF PAYMENT FOR REGISTRATION / ACCOMMODATION PACKAGE

Payment can be effected either:

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

- To Alpha Bank to the order of ERA Ltd Account No: **101.00.2002044307**,
IBAN Code: GR 660140 1010101002002044307

Charges to be paid by sender

Please enclose a copy of transfer receipt with the form.

b) By major credit cards. Please complete the relevant information as described below.

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

WEB SITE

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

www.msrmmeetings.com

SECRETARIAT AND TRAVEL AGENCY

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



ERA Ltd.

17, Asklipiou Str., 106 80 Athens - Greece

Tel.: +30 210 3634944 • Fax: +30 210 3631690

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ORAL PRESENTATIONS



TRANSVAGINAL ULTRASOUND AND PELVIC ENDOMETRIOSIS

Stratoudakis G., Patramani S., Tzitzikalakis C., Zouridis A., Daskalakis G.

Department of Obstetrics & Gynecology of General Hospital of Chania, Kriti, Greece

Background: The development of non-invasive techniques to establish the presence and severity of pelvic endometriosis is valuable to guide patient choice regarding medical or surgical treatment, to plan fertility or medical treatment if surgery is not chosen and to allow the surgeon to prepare sufficiently for surgery, including the involvement of other specialties as indicated.

Aim: To establish whether transvaginal ultrasound (TVS) is a reproducible technique for preoperative assessment of the severity of pelvic endometriosis.

Methods: Women with clinically suspected or proven pelvic endometriosis were invited to join the study before surgery. All patients included underwent TVS performed by two observers and a laparotomy assessment of pelvic endometriosis.

Results: In the 2-year period from 2012 to 2014, 19 patients were recruited to the study and all received a TVS examination performed by two ultrasound observers. Of these patients, one cancelled laparoscopy and was therefore excluded from the final analysis. The mean age of the patients at recruitment was 33.8 (range, 18-51) years. The principal presenting symptoms were: dysmenorrhea (16/18; 88.8%), dyspareunia (10/18; 55.5%), chronic pelvic pain (11/18; 61.1%), infertility (6/18; 33.3%), dyschezia (5/18; 27.7%) and cyclic rectal bleeding (1/18; 7.1%). At laparotomy, no endometriosis was found in 6 (33.3%) of these patients, one (5.5%) had minimal disease, one (5.5%) had mild disease, 3 (16.6%) had moderate disease and seven (38.8%) had severe disease.

Conclusions: TVS is a reproducible method for assessment of the severity of pelvic endometriosis and shows good agreement with findings on surgery.

References:

1. Holland TK, Yazbek J, Cutner A, Saridogan E, Hoo WL, Jurkovic D. Value of transvaginal ultrasound in assessing severity of pelvic endometriosis. *Ultrasound Obstet Gynecol.* 36(2):241-8;2010.
2. Bazot M, Darai E. Value of transvaginal sonography in assessing severe pelvic endometriosis. *Ultrasound Obstet Gynecol*36(2):134-5;2010

METHODS OF EMERGENCY CONTRACEPTION

Stratoudakis G., Patramani S., Tzitzikalakis C., Zouridis A., Daskalakis G.

Department of Obstetrics & Gynecology of General Hospital of Chania, Kriti, Greece

Background: Methods of emergency contraception represent the only options to reduce the risk of unintended pregnancy following unprotected intercourse.

Aim: To compare the pregnancy rates for one year following presentation for emergency contraception in women who selected either oral ulipristal acetate or the multifiload IUD for emergency contraception.

Methods: Women presenting for emergency contraception at the family planning clinic in Chania, Kriti were offered participation in this study comparing oral ulipristal

acetate or the multiload IUD for emergency contraception from November 2013 to July 2015. Study participants were age 18-30 years and had unprotected intercourse within 120 hours of presenting.

Results: There were 274 women who presented to our clinic requesting emergency contraception and were willing to participate in the study: 109 women who choose the multiload IUD and 165 selected oral ulipristal acetate. From the demographics characteristics, women choosing the IUD were older, more likely to be uninsured, and were more likely to have heard of the IUD prior to their clinic visit than those choosing oral ulipristal acetate. In both groups, more than 1/3 of women were not using any method of contraception when they presented for emergency contraception (35% in the IUD group and 42% in the oral ulipristal acetate group).

Conclusions: Twelve months after presenting for emergency contraception women who initially selected the copper IUD for emergency contraception were more likely to be using highly effective contraception and less likely to report having had a pregnancy than those who selected oral ulipristal acetate.

References:

1. Koyama A, Hagopian L, Linden J. Emerging Options for Emergency Contraception. *Clin Med Insights Reprod Health.* 7:23–35;2013.
2. Moreau C, Trussell J. Results from pooled Phase III studies of ulipristal acetate for emergency contraception. *Contraception.* 86(6):673–680;2012.
3. Cleland K, Zhu H, Goldstuck N, Cheng L, Trussell J. The efficacy of intrauterine devices for emergency contraception: a systematic review of 35 years of experience. *Hum Reprod.* 27(7):1994–2000;2012

O.P. 03

SPONTANEOUS ABORTION AND RECURRENT MISCARRIAGE: A COMPARISON OF CYTOGENETIC DIAGNOSIS IN 198 CASES

*Kontodiou Maria*¹, *Siomou Eliza*¹, *Siahami Anthoula*¹, *Karambournioti Evangelia*², *Malathrakis Dimitrios*², *Papoulidis Ioannis*¹, *Manolakos Emmanouil*¹

¹Access To Genome (ATG) Labs, Athens - Thessaloniki

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OBJECTIVE:

The purpose of this study was to determine the frequency and distribution of cytogenetically abnormal miscarriages in couples with spontaneous abortions (SA) or recurrent miscarriages (RM).

METHODS:

Karyotyping of specimens from 112 abortuses with SA and 86 abortuses with RM was successfully performed according to the standard cytogenetic methods using G-banding technique.

RESULTS:

Among the total 164 cases of SA group, 81 (49.4%) were euploid and the rest (83, 50.6%) showed chromosomal abnormalities. In RM(≥ 2) and RM(≥ 3) group, 31 (36.0%)/27 (34.6%) cases were euploid and 55 (64.0%)/51 (65.4%) cases were abnormal, respectively. A statistically significant difference was found in the rate of cytogenetic abnormality between SA and RM groups ($P < 0.05$). In all groups, women with advanced maternal age (≥ 35 years) had a higher rate of chromosome anomalies compared with women younger than age 35 (normal:abnormal = 32.4%:67.6% for

≥35 years and 53.8%:46.2% for <35 years in SA; 19.2%:80.8%/21.7%:78.3% for ≥35 years and 43.3%:56.7%/40.0%:60.0% for <35 years in RM(≥2) and RM(≥3), respectively; $P < 0.05$). In SA group, an increase of normal karyotypes was noted with increased gestational age (<10 week, 38.0%; 10-15 week, 53.5%; 16-20 week, 65.7%). In RM group, most of cases were in <10 week and the frequency of trisomies with chromosomes 1 to 10 were increased compared with that of SA.

CONCLUSION:

There was a statistically significant difference in the frequency and distribution of chromosomal abnormalities between SA and RM groups. Our results will provide useful information for diagnosis and genetic counseling of patients with SA or RM.

O.P. 04

THROMBOPHILIC AND FIBRINOLYTIC DEFECTS IN PCOS WOMEN WITH RECURRENT MISCARRIAGES

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Objective: To compare the prevalence of thrombophilic and fibrinolytic defects in PCOS women with recurrent miscarriages (RM) and in regularly menstruating women with RM.

Materials and Methods: In this case-control study, we enrolled 28 women with PCOS and a history of ≥ 2 pregnancy losses and 96 women with normal ovarian function and a history of ≥ 2 pregnancy losses. In these two groups, we compared the prevalence of factor V Leiden, prothrombin G20210A factor, and methylene tetrahydrofolate reductase (*MTHFR*) mutations, as well as protein C, protein S, antithrombin III deficiencies, factor XII deficiency and elevated plasminogen activator inhibitor activity.

Results: Thrombophilic defects were found in 67% of PCOS women with RM and 75% of regularly menstruating women with RM (P =non significant), whereas fibrinolytic defects were found in 61% of PCOS women with RM and 36% of regularly menstruating women with RM ($P=0.03$).

Conclusions: Fibrinolytic defects are significantly more common in PCOS women with RM than in women with normal ovarian function and RM. Thrombophilic factors do not show increased prevalence in PCOS women with RM in comparison with regularly menstruating women with RM.

O.P. 05

OXIDATIVE STRESS UPREGULATES A-TOCOPHEROL TRANSFER PROTEIN IN HUMAN TROPHOBLAST TUMOR CELLS

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Abstract

α -Tocopherol transfer protein (α -TTP) is the intracellular transport protein for the antioxidant vitamin E (α -tocopherol). Herein, we investigated whether placental expression of α -TTP could be modified by inducible oxidative stress. The human choriocarcinoma cell line BeWo was, thus, treated with two known pro-oxidants and α -TTP expression was evaluated by immunohistochemistry. It was found that oxidative stress could significantly upregulate α -TTP expression, a fact that could be explained as part of a rescue mechanism of the placental cells against oxidative stress, aiming mainly to the intracellular increase of α -tocopherol. Since oxidative stress is part of normal and pathological placentation, α -TTP seems a reasonable target for further studies of early and ongoing pregnancy.

O.P. 06

PROTECTIVE AND RISK FACTORS OF SUCCESSFUL IN-VITRO FERTILIZATION OUTCOME: PRELIMINARY RESULTS

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Abstract

Background: Abundant of research evidence (e.g., De Klerk et al., 2008; Ebbesen, 2009; Li et al., 2011) suggests that various psychosocial factors may affect the outcome of in-vitro fertilization (IVF). However, the influence of these factors on the outcome of IVF treatment is not well known.

Aim: The examination of the psychosocial factors affecting successful IVF outcome.

Methods: A sample of 61 infertile women (Mean age 37.2) undergoing IVF treatment was administered a questionnaire with measures of various psychosocial factors.

Results: Over half of them (50.8%) became pregnant. A stepwise logistic regression analysis was conducted on pregnancy as the outcome, with age, known or not-known cause of infertility, infertility stress, coping mechanisms, personality type, sense of control, quality of marriage/relationship, psychological resilience, well-being (i.e. positive relationships, self-acceptance, autonomy, personal development, environmental control, life purpose), life satisfaction, and emotions (positive and negative) entered simultaneously as predictors. The model was statistically significant (Omnibus Chi-square=27.324, df=5, $p<.001$) and accounted for 40.9%-54.7% of the variance. Overall 84.6% of the predictions were accurate. Life purpose and negative emotions

(e.g., discontent, sorrow) increased pregnancy rates, whereas autonomy, personal development and stress decreased pregnancy rates.

Conclusions/Implications: The relationship between psychosocial factors and successful IVF outcome is more complex than commonly believed. A number of risk and protective factors in infertile women may diversely affect IVF outcome, the identification of which could contribute to increased pregnancy rates and also foster the implementation of tailored therapeutic interventions. More research is required to evaluate psychosocial factors in male partners too.

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O.P. 07

PRODROMAL PRIMARY OVARIAN INSUFFICIENCY WITH INTERMITTENT OVARIAN FUNCTION IN A 19-YEAR-OLD WOMAN PRESENTING WITH SECONDARY AMENORRHEA

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Introduction: The median age of women with primary ovarian insufficiency (POI) is 32 years. Here we present a case of prodromal primary ovarian insufficiency with intermittent ovarian function in a 19-year-old woman presenting with secondary amenorrhea.

Case: The patient presented with secondary amenorrhea at age 19 years. The duration of amenorrhea was 18 months. No positive medical history was noted regarding smoking, chemotherapy, radiation or autoimmune diseases and the physical examination was normal. There was no family history of POI. She reported a spontaneous menstrual cycle after receiving corticosteroids for an allergic reaction. Measurements of gonadotropin levels on two occasions (3 months apart) showed elevated FSH and LH levels, whereas estradiol levels were low in the first occasion and normal in the second. TVS showed a cyst in the left ovary. The karyotype test was normal. AMH levels were low. During the evaluation the patient had two spontaneous menstrual cycles (without any medical intervention).

Conclusion: POI is a heterogeneous condition that involves medical concerns regarding bone and cardiovascular health, emotional well being, and sexuality of the affected patients. Approximately half of the patients have intermittent ovarian function. Management should be directed at symptoms resolution, bone protection, and psychosocial support for women facing this unexpected and devastating diagnosis.

THE ROLE OF DECIDUAL MACROPHAGES IN SPONTANEOUS ABORTION: UP-REGULATION OF FASL EXPRESSION

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Abstract

Decidual macrophages (DM) are one of the most abundant populations in the fetal-maternal interface. Tissue samples from cases of spontaneous miscarriages and elective terminations of pregnancy were assessed by immunohistochemistry and dual immunofluorescence for evaluating DM density and FasL expression. It was found that in spontaneous miscarriages not only the DM are significantly increased, but they also overexpress FasL. We believe that, in case of spontaneous abortions, such alteration in DM population is enhancing an inflammatory profile in favor of an M1 immuno-phenotype. Further better powered studies are expected to highlight such a role for DM and clarify their clinical significance in abortion pathophysiology.

ELEVATED CSF-1 EXPRESSION BY THE EUTOPIC ENDOMETRIUM OF WOMEN WITH ENDOMETRIOSIS: EVIDENCE OF CRH/UCN-MEDIATED CSF-1 UPREGULATION

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The role of Colony Stimulating Factor-1 (CSF-1) is well established as supporting implantation. The aim of this study was to investigate CSF-1 protein expression levels in women with endometriosis. Additionally, it was investigated whether CRH and UCN affect CSF-1 expression levels in vitro. Eutopic endometrium specimens from healthy women as well as both eutopic and ectopic endometrium specimens from women with endometriosis were retrieved from archival materials. The Ishikawa cell line and mice macrophages were used for the in vitro experiments. We have shown for the first time that: a) CSF-1 was overexpressed in the eutopic endometrium of women with endometriosis compared to healthy controls and b) CSF-1 expression was further overexpressed by the ectopic endometrium compared to the eutopic endometrium of women with endometriosis. Additionally, we have presented the first evidence that CSF-1 expression may be regulated by the neuropeptides CRH and UCN. All the data taken together, imply a de-regulated inflammatory profile in case of endometriosis, supporting the establishment and the maintenance of the disease and contributing to a local immune profile being against implantation. The fact that CSF-1 up-regulation was in vitro inhibited by antalarmin, could make CRHR-1 inhibition an appealing anti-inflammatory approach in controlling endometriosis.

**INVITED SPEAKER'S
ABSTRACTS**



ROUND TABLE 1

«CONTRACEPTION: WHAT IS GOOD CLINICAL PRACTICE?»

ADOLESCENCE - NEW ORAL CONTRACEPTIVES AND HPV INFECTIONS

Prof. G. CREATSAS, MD FACS FRCOG FACOG

During the last years an effort was undertaken to reduce ethinyl estradiol (EE) dose. These studies were associated with increased tolerability. However, as the dose of EE was reduced, the cycle control was compromised. On the other hand early attempts to develop 17 β estradiol (E₂) based combined oral contraceptives (COCs) accompanied with high rates of prolonged and heavy bleeding and high rates of amenorrhea with a consequence of high rates of discontinuation. As there were indications that EE was responsible for several side effects of COCs, related to liver function, venous thromboembolism and hypertension, research was directed towards to develop COCs with 17 β estradiol and new progestagenic compounds as the dienogest, drospirenone, megestrol acetate and other progestagen. Emphasis has given to the new progestagenic compounds with both progestagenic and antiandrogenic efficacy.

Furthermore the non contraceptive benefits of the new generation COCs were taken into account as the acne, the regulation of menstrual disturbances, the prevention of endometrial and the ovarian cancers, the prevention of ovarian cysts, the endometriosis, the pelvic inflammatory diseases, the bone mass, the polycystic ovarian disease, the liver function and the improvement of lipid profile.

The beneficial effects on the endocrine – biochemical and haemostatic markers, the thyroid function, the adrenal indices, the effect on SHBG, the improvement of haemostasis and inflammation markers, as well as the favorable effects on the lipid and carbohydrate metabolism have been also reported.

EMERGENCY CONTRACEPTION

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Emergency contraception (EC) is one of the main tools to avoid unintended pregnancies; the latter consist an important public health problem worldwide, as they may end in induced abortion or unwanted childbirth, both linked with various socio-economic and psychological problems.

There are different interventions available, used shortly after unprotected intercourse, in the form of molecules and techniques, including the Yuzpe regimen, mifepristone, levonorgestrel (LNG) and ulipristal acetate (UPA), and the copper intrauterine device (Cu-IUD). Information on the comparative effectiveness, safety and convenience of these methods is crucial for reproductive healthcare providers and the women they serve. It is important to say that all of them have been proven generally safe and well tolerated by the users. Nausea and vomiting are more frequent in

oestrogen-containing EC methods and changes in subsequent menses are mainly caused by progestogen and anti-progestogen methods. LNG users are more likely to have a menstrual return before the expected date, but UPA users are more likely to have a menstrual return after the expected date. Menstrual delay is the main adverse effect of mifepristone and seemed to be dose-related. Concerning their way of EC, while the main effect of both available ECs is to prevent or delay ovulation the window of action for UPA is wider than that of LNG. This provides the biological explanation for the difference observed in clinical trials and the higher efficacy of UPA. Neither LNG nor UPA impairs endometrial receptivity or embryo implantation.

Cu-IUDs are a highly effective method of EC, safe for the majority of women, and cost-effective when left in place as ongoing contraception, after unprotected intercourse. The maximum timeframe from intercourse to insertion is reported from 2 days to 10 or more days, while the pregnancy rate is 0.1%.

In a Cochrane systematic review, published 3 years ago, including 100 trials with 55,666 women, concluded that intermediate-dose mifepristone (25-50 mg) was superior to LNG and Yuzpe regimens. Mifepristone low dose (< 25 mg) may be more effective than LNG (0.75 mg two doses), but this was not conclusive. UPA may be more effective than LNG. LNG proved to be more effective than the Yuzpe regimen. The Cu-IUD was the most effective EC method and was the only EC method to provide ongoing contraception if left in situ.

Additionally, advance provision of EC through these methods, while, a summary estimate (RR 0.90, 95% CI 0.69-1.18) of four RCTs did not demonstrate a significant reduction in unintended pregnancy over 12 months when advance provision was compared with standard provision of EC. Patterns of contraceptive use, pregnancy rates and incidence of sexually transmitted infections did not vary between treatment and control groups in the majority of studies among either adults or adolescents.

In low- and middle-income countries, there are a number of gaps in the research concerning service delivery; these include a lack of knowledge concerning private/commercial sector contributions to improving access, the needs of vulnerable groups of women, approaches to enhancing intersectoral collaboration, evidence for social marketing models and investment cases for EC.

Recently, prostaglandin-endoperoxide synthase 2 (PTGS2) enzyme (also known as cyclooxygenase-2 or COX2) PTGS2 inhibitors alone have emerged to be used as EC. Inhibitors of additional PGE2 synthesis enzymes or modulation of PGE2 metabolism or transport also hold potential for reducing follicular PGE2 and preventing ovulation.

CONTRACEPTION IN ADOLESCENCE

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Introduction

Adolescence, is a period in which numerous corporal, cognitive and psychological changes occur in a relatively small time window. As a result, in the context of these changes adolescent sexuality develops. During the first years of a teen's sexual life, the lack of experience, combined many times with inadequate counselling and

knowledge may result in serious health consequences including unintended pregnancies and acquisition of Sexually Transmitted Infections (STIs).

In developed countries, a significant percentage of young women initiate their sexual life before the age of 19. In the USA, this percentage is 42% according to data from 2008, presented by the ACOG.¹ According to Allan Guttmacher Institute², the above mentioned percentage reaches 71%. Data, regarding age at initiation of sexual life in Greece are sparse, with very few studies having been published. In one study including young women of higher education aged between 18 and 26 years, reported that about half of women have their first intercourse before the age of 17.³ According to another study in both male and female pupils aged 14 to 16 years, the percentage of sexually active adolescents was as high as 73%.⁴ Given that these studies were performed during the last years, it seems that age of first sexual intercourse has declined in the last years. It is therefore essential to take action, regarding sexual education in Greece, in order to ensure that they have access to proper sexual education including contraception and protection against STIs.

According to the Allan Guttmacher Institute², each year almost 615,000 U.S. adolescents aged 15–19 become pregnant (6% of adolescents), with two-thirds of all teen pregnancies occur among the oldest teens (18–19-year-olds). Despite that the vast majority of pregnancies (82%) are unplanned, only 26% of them end in an abortion. Data regarding abortions are unfortunately not available in Greece, but estimations can be made considering the percentages of abortions in the European Union. The highest adolescent abortion rate is observed in England, Wales and Sweden (2% of adolescents compared to USA with a percentage of 1.5%). In about half of the countries, the rate was between 0.8 and 1.7%, with the lowest teen abortion rate being observed in Switzerland.

All these data that have been published during the recent years despite the widespread use of oral contraceptive pills in the western countries, demonstrate that with typical use, neither the condom, nor the oral contraceptive pills have succeeded to reduce unwanted pregnancies and abortions. In the light of these findings, medical organizations including the Center for Diseases Control (CDC), the American Academy of Pediatrics, the American College of Obstetricians & Gynecologists (ACOG) and the National Institute for Health and Care Excellence (NICE) have issued guidelines, which state that there is a need for more efforts in order to offer to adolescents proper sexual education and access to sexual health services. Additionally, they recommend that Intrauterine Devices (IUDs) and Contraceptive Implants (which are referred as Long Acting Contraception – LARC) should be considered a first line option for contraception in adolescence, as they can erase the factor of reduced compliance, which seems to be the main problem in this age group.^{1,5,6,7}

Contraceptive choices in adolescence: What teens use nowadays

Nowadays, the most popular contraceptive methods used by adolescents include withdrawal, the male condom and the oral contraceptive pill. Other contraceptive choices which are in use in western countries but have very little (if any) use in Greece include the Depot-medroxyprogesterone acetate (DMPA) injection, the contraceptive patch, the vaginal ring, as well as other barrier methods like the diaphragm and the cervical cup. These methods are also considered to be short-acting methods, and therefore highly depending on the users' compliance, making them inappropriate for use in adolescents.

Withdrawal is unfortunately, very popular among adolescents in Greece, with reported rates as high as 40%.⁴ Due to very high failure rates, clinicians should never forget to pose specific questions about withdrawal use when counseling an adolescent.

The male condom use has low cost, great accessibility and is one of the most popular methods, which offers the best protection against STIs. In Greece, about 80% of ado-

lescents report using it during their first sexual intercourse. Although the failure rate with perfect use of male condoms is 2%, the typical use failure rate is 18% for all users and can be higher among adolescents. Unfortunately, continuation of use is far from ideal with about half of the users continuing to use the method after one year. Nevertheless, the American Academy of Pediatrics, suggests the combined use of male condom together with a highly effective hormonal or other long-acting contraceptive method, due to the condom's high STIs protection, along with the high typical use failure rate. The Combined Oral Contraceptives (COCs) are the third most popular method used worldwide. Despite keeping the same place in Greece, the percentages of use are far lower than other western countries. COCs use in Greece is calculated to be below 10%, while in most of the western countries percentages as high as 50% are noted. They are highly effective with consistent use, with about 0.1% failure rate, but the need for a daily dosage makes the failure rates with typical use at 6-8%, which may be higher among adolescents. The safety profile of COCs has been studied extensively during the last 50 years since their invention by G. Pincus. They have few contraindications in healthy female adolescents which include severe and uncontrolled hypertension, ongoing hepatic dysfunction, complicated valvular heart disease, migraines with aura or focal neurologic symptoms, thromboembolism and complicated diabetes. Although smoking should be discouraged, it is not a contraindication to COCs use in teenagers and adults younger than 35 years old.⁹ The most serious adverse event associated with COCs use is the increased risk of thromboembolism, which increases from 1 per 10 000 in non-users to 3 to 4 per 10 000 woman-years during COCs use. COCs have also well-established benefits, besides contraception. They offer protection against endometrial, ovarian and colorectal cancer. They are considered a first line treatment for menstrual disorders in adolescence and can be used as treatment for hirsutism, acne, dysmenorrhea and endometriosis. In fact, a significant percentage of adolescents using oral contraceptives, have initiated them for other reasons than contraception, mainly for managing menstrual-related disorders.

Long Acting Reversible Contraception (LARC): The future of adolescent contraception

Intrauterine Devices (IUD) are inserted into the uterine cavity, providing longtime contraception. There are currently two intrauterine devices available for use in Greece. One copper-containing IUD, and the levonorgestrel releasing IUD. Intrauterine devices have an effect in sperm motility as well as in the endometrium which result in preventing fertilization and implantation. Despite past concerns, IUD are now considered safe for nulliparous adolescents and have not been associated with fertility problems after removal. Moreover, there has been no evidence that IUD increases the risk of Pelvic Inflammatory Disease, with a small increase occurring only in the first 20 days post insertion. There are very few contraindications for its use and are limited to current purulent cervicitis, gonorrhea or chlamydia infection and current PID, while neither past PID, nor HIV infection are contraindications to IUD use. Its safety profile can make it ideal for obese adolescents, as well as for adolescents with chronic complex medical problems. The main concern, regarding its use in adolescence, is the risk of expulsion due to the reduced dimensions of the nulliparous uterus. Studies show an elevated risk in comparison with adults, but these studies have been performed with older type IUDs which were constructed based on non-accurate anatomical models of the uterine cavity. Newly available IUDs with reduced dimensions may reduce this risk, but extensive studies have not been published yet. Another concern is the risk of menstrual abnormalities which can be present in the first months of use, while health care providers should counsel adolescents that amenorrhea, spotting or irregular bleeding may be present in the first months of use, so they understand that these changes are expected.

The Progestin Implant contains etonogestrel and is inserted into the inside of the upper arm, with a special device. It may remain in place for up to 3 years providing highly effective contraception, with typical and perfect use failure rates of less than 1%. This method is ideal for adolescents as it provides an extended length of protection without requiring regularly scheduled adherence. The contraceptive implant has also secondary health benefits, since the reduced amount of blood loss can lead to higher hemoglobin levels. Moreover it reduces dysmenorrhea and pelvic pain, while it has no effect in bone mineral density and in body weight. A significant problem associated with implant use is the occurrence of menstrual irregularities which can range from ammenorhea to prolonged and frequent bleeding. Adolescents need to be counseled regarding this side-effect, as anticipatory guidance regarding bleeding patterns may improve satisfaction and continuation.

Conclusion

Counseling and education are the most important weapons against unwanted pregnancies and abortions in adolescence. This counseling should include information about all contraceptive methods that are safe and appropriate for them with particular focus in methods that have been proven to be efficient. Among them, the cornerstone should be the male condom which is the only method that can provide adequate protection against STIs. It should be clear that the adolescents have to use it during every sexual intercourse, in combination with a hormonal or a Long Acting Reversible Contraceptive methods.

The choice of the method depends on other problems that may be present, like menstrual irregularities, Polycystic Ovarian Syndrome, which can be adequately managed for their use except contraception. Moreover, when coping with an adolescent with multiple and chronic illnesses, clinicians should not overlook their sexual health and contraceptive needs, which are similar to healthy adolescents and choose an appropriate contraceptive method.

Another issue that is often overlooked when dealing with adolescent patients is the up keeping with the adolescent's sexual history. Careful notes should be taken with every appointment with the teen while the doctor stays non-judgmental, while addressing to the adolescents' needs for contraception, STI screening, and sexual risk reduction counseling.

Finally, when choosing contraceptive methods, adolescents should be encouraged to consider LARC methods like IUDs and the implant, which are considered first-line contraceptive choices.

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CONTRACEPTION IN PERIMENOPAUSE

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Perimenopausal women have low fecundity rates due to anovulation and poor oocyte quality, but when pregnant their pregnancies are at high risk, while a great proportion of these unintended pregnancies are terminated. Therefore, contraception in this age group is rather relevant and significant. However, with increasing age, the background risk of medical morbidities increases and may be further intensified with some contraceptive methods. For example, the effects of contraception on cardiovascular risk, breast cancer, and loss of bone mineral density are of particular significance. On the other hand, hormonal contraception offers some non-contraceptive health benefits such as cycle control and improvement of heavy menstrual bleeding, alleviation of menopausal symptoms, and reduction of ovarian and endometrial cancer risk. No method of contraception is contraindicated by age alone, however it is important that each individual woman should weigh up the benefits and risks of a particular contraceptive method. Finally, it should be stated that hormone replacement therapy is not reliable contraception and women should be advised to continue with a contraceptive method until they have reached the menopause.

ROUND TABLE 2:

«COMBINED ORAL CONTRACEPTIVES: RISKS AND BENEFITS»

ORAL CONTRACEPTIVES AND CARDIOVASCULAR RISK

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Cardiovascular disease, including coronary artery disease, stroke, and peripheral vascular disease, is the leading cause of death among women. Epidemiologic studies established that first-generation oral contraceptives (OCs), containing 50 µg or more of estrogen combined with a progestogen, increased the risk of venous thromboembolism, stroke, and myocardial infarction. Subsequent formulations have contained <50 µg of estrogen and have been associated with lower cardiovascular disease risk. However, OCs containing the third-generation progestins desogestrel and gestodene have been associated with greater risks of venous thromboembolism than are associated with older progestins.

The risk of cardiovascular disease is increased among users of OCs who smoke, particularly those who are ≥ 35 years old or carry the coagulation factor V Leiden mu-

tation. Other important cardiovascular disease risk factors in women include hypertension, waist/hip girth ratio >0.8, dyslipidemia, glucose values ≥ 100 mg/dL, lack of physical activity, and high-fat diet. The decision to use hormonal contraceptives and the choice of formulation should be individualized based on patient's age, smoking history, obesity, history of diabetes, hypertension, dyslipidemia, thrombophilia, and personal or family history of a venous thromboembolic event.

In the absence of a history of smoking and other conventional risk factors, current or former OC users do not appear to have an increased risk of cardiovascular disease. Oral contraceptives (OCs) is one of the most effective birth control methods and one of the most commonly prescribed worldwide. Most OC users are young and healthy with a low background incidence of major disease; for these women the use of OCs is safe.

OPENING LECTURE

VIOLENCE AGAINST WOMEN – WHAT THE GYNECOLOGIST SHOULD KNOW

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In all societies, to a greater or lesser degree, women and girls are subjected to physical, sexual and psychological abuse that cuts across lines of income, class and culture¹. A WHO review of studies from 35 countries indicated that between 10 and 52 percent of women were physically abused at some point in their lives and that between 10% and 27% of women and girls reported having been sexually abused either as children or adults².

Violence against women (VAW) can start before she is even born and can take several forms. These include (1) selective feticide, (2) female genital mutilation – FGM, (3) honor crimes, (4) rape, (5) sexual harassment, (6) trafficking in women, (7) mugging senior citizens as well as (8) domestic (intimate partner) violence. Each of these forms can be physical, emotional, verbal, sexual or economic. VAW can result in serious physical and psychological health problems and is also a public health concern.

Professor Amartya Sen, the Nobel laureate in economics of 1998 argues that up to 100 million women may be missing from today's world due to selective feticide, practiced mainly in India and China^{3,4}. Inducing abortion in these cases can result in various complications including infection in 27 % of cases, subsequent infertility in 3 to 5 % of cases, a 5 – to 8-fold increased risk of ectopic pregnancy, a 3- to 5-fold increase in premature birth due to cervical damage⁵, in addition to various psychological sequelae including depression, loss of self-esteem, self-destructive behavior, sleep disorders and memory loss⁶.

FGM is another crime prevalent in the Nile basin and some neighboring countries. A WHO study conducted in 2006 on 28,393 women in 28 obstetric centers in six African countries reported an increased risk of death to the baby (15% for Type I, 32% for Type II, and 55% for Type III), and increased risk of cesarean section (30%) and an increased risk of postpartum hemorrhage (70%)⁷.

The so-called honor crime is another form of VAW. The United Nations Population Fund (UNFPA) estimates that the annual worldwide total of honor-killing victims may be as high as 5,000. These crimes take place mainly in Egypt, Jordan, Lebanon, Morocco, Pakistan, Syria, Turkey, Yemen and other Mediterranean and Gulf countries,

as well as in the immigrant communities in France, Germany and the UK⁸. Rape is the ultimate crime against women, but is also the least reported. A UN report from 65 countries showed that more than 250,000 cases of rape or attempted rape are reported annually and that many more are never reported for fear of loss of reputation or retaliation⁹. In the USA, it is estimated that only 16% of rapes and sexual assaults are reported to the police¹⁰. Besides injury, bleeding, acute stress disorder, post-traumatic stress disorder of various degrees of severity, rape can also result in an unwanted pregnancy (and subsequently complications of abortion) as well as sexually transmitted diseases including AIDS. Rape has also been used as a weapon of war and it has been estimated that about 250,000 to 500,000 women were raped during the 1994 Rwandan Genocide¹¹. Trafficking in women is another form of VAW and is considered a form of modern-day slavery. In a study by the London School of Hygiene & Tropical Medicine conducted in 2003, all trafficked women studied were found to have been sexually abused and coerced into involuntary sexual acts, including rape. Gynaecological complications were common and 25% of them had at least one unintended pregnancy and a subsequent abortion¹². Domestic (or partner) violence is another form of VAW which can result in injury, psychological trauma, disability and even death. In another WHO report published in 2004, VAW was perpetrated by their partners in 15 to 91 percent of cases, but only 5 to 45 percent of them sought help¹³. It was also found that up to 70% of female murder victims are killed by their male partners¹³. Finally, VAW is a public health concern. A World Bank report estimated that rape and domestic violence account for about 5% of the total disease burden among women aged 15-44 in developing countries¹⁴.

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THE DILEMMA TO CHOOSE THE FSH STARTING DOSE IN IVF

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Ovarian stimulation is a challenging experience. Even the most experienced endocrinologist may fail to reach optimum ovarian response without OHSS or cycle cancellation. Reaching the optimum dose requires clinical experience and strong scientific background, extreme knowledge of the factors which determine ovarian response. The basis upon which you decide starting dose of FSH and how to avoid OHSS or cycle cancellation vary from age, response in previous stimulation cycle, ultrasound criteria, hormonal profile, weight and BMI, and other personal factors.

Younger patients require smaller doses of FSH, while older patients require larger doses. However, there is no fixed rule, sometimes older patients respond strongly to smaller doses.

Ultrasound criteria include Size of ovary: more than 10 ml, Antral follicle count: 12 or more in each ovary are highly suggestive of strong response and Small ovaries with few AF count suggest poor response.

FSH assay has some drawbacks. It must be done in early follicular phase. High FSH may demonstrate poor ovarian response and menopause and normal FSH level does not accurately represent ovarian reserve.

AMH is the most informative serum marker of ovarian reserve that can be assessed at any point in the cycle. It is the most predictive factor for number of oocytes retrieved during IVF. It helps to avoid cancellation of cycles and it helps to determine the dose of FSH required for stimulation. It can also detect possibilities of poor response. It is a good marker after chemotherapy for cancer and a good marker for occurrence of menopause. It can be done any day of the cycle.

Obesity has a significant negative effect on ART outcome. Patients with BMI > 30 Kg/m have up to 68% lower odds of having live birth rate following ART. Obese women require higher doses of medication and produce fewer follicles for a given dose, but once medication and response are adjusted to overcome the weight effect the success of treatment is comparable to normal weight women. AMH levels are significantly lower by 34% in obese women.

Starting dose of FSH in IVF for PCOS patients should always be small. 100-150 IU is the maximum dose use.

It is well established that, in general, ovarian reserve declines with age. However, the rate of this decline seems to vary among individuals and depends on the medical history and various environmental and genetic factors. It is possible that women who do not respond well to a relatively low dose of gonadotrophs will respond better to a higher dose, but it has been shown that increasing the dose beyond a certain level rarely improves the outcome. Increasing the stimulation dose of rFSH in unexpected poor responders is not associated with better IVF outcome. Poor responders are not a homogeneous group of women with regards to pregnancy prospects. Female age and number of oocytes retrieved in particular will modulate the chances for pregnancy in current and subsequent cycles.

In conclusion, the dose of FSH required for ovarian stimulation in IVF/ICSI, depends

upon age, previous ovarian response, AMH level, ultrasound findings and weight. Optimizing ovarian stimulation is achieved by avoiding cycle cancellation and OHSS. PCOS patients and poor responders require special stimulation dose.

IMPROVING LIVE BIRTHS RATES IN POOR RESPONDERS. STIMULATION PROTOCOL STRATEGIES. THE ROLE OF HCG

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The response of several patients to ovarian stimulation protocols used as a routine is not always as expected. A failure to respond adequately to standard protocols and to recruit an adequate number of follicles is called 'poor response'. The lack of clear, uniform definition concerning the poor responders and the lack of large-scale randomized studies make data interpretation very difficult for precise conclusions.

Optimistic data have been presented with the use of high doses of gonadotropins rFSH or HMG , the flare up Gn RH-a protocol(standard or microdose), the stop protocols, the luteal onset of Gn RH-a and the short protocol. The use of GnRH antagonist may be associated with simpler stimulation protocols, lower gonadotropin requirements, reduced patient costs, and shorter downtimes between consecutive cycles. Recent data suggest a potential beneficial effect of aromatase inhibition by the administration of letrozole prior to gonadotropin stimulation. Growth hormone and pyridostgmine in poor responders has been found to show a significant improvement in live birth. There is evidence that sort term pretreatment with transderm testosterone or long term treatment with DHEA has beneficial effect in poor responders. Also low dose of aspirine , adjunctive use of L-arginine ,and glucocortoids administration are alternative therapeutics approaches but further trials are needed to support the beneficial effect in patients confirmed as poor responders.

A recent Duplex protocol features , during the follicular and luteal phases in the same menstrual cycle provided more opportunities to retrieve oocytes in poor responders, with the resulting embryos having similar development potential. Double stimulation and subsequent cryopreserved embryo transfer is a promising approach both for patients with poor response, especially for the cases that repeatedly did not have oocytes retrieved or viable embryos using conventional IVF regimens.

The use of hCG in ovarian stimulation in IVF-ET cycles has a beneficial effect in the quality of oocytes, as well as in the pregnancy rate.

The LH/hCG receptor has an almost ubiquitous distribution in reproductive organs, thus suggesting that the actions of hCG might be more extensive than previously thought. Independently of follicular stimulation hormone (FSH), low dose hCG can support development and maturation of larger ovarian follicles that have acquired granulosa cell LH/hCG receptors, potentially providing effective and safer ovulation induction regimens.

Recently study have been conducted from our unit shown that the addition of hCG to rFSH in a short GnRH-agonist protocol, throughout the follicular phase, had a beneficial effect in terms of pregnancy rates. Furthermore, hCG was associated with better quality embryos. The significance of these findings was accentuated by the fact that women, who received hCG were significantly older and with higher basal FSH levels, thereby with expectant poorer ovarian reserve. Among the underlying explanations, hCG interaction with LH/CG receptors developed in granulosa cells of

larger antral follicles, which can enhance follicle growth and maturation as well as hCG properties in improving endometrial environment and subsequently implantation potential should be stressed. In fact, hCG-mediated LH activity sounds quite attractive due to its long acting profile, which can provide more prolonged and stable stimulation of LH/CG receptors compared to other means of LH activity.

SESSION II

WHAT IS THE BEST APPROACH FOR SEVERE ADHESION. SHOULD WE TREAT BEFORE IVF ?

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Severe adhesions are quite common in infertile patients. There are roughly three situations where severe adhesions may be expected:

- after any surgical procedures but more often in case of myomectomy
- on PID patients
- on patients with endometriosis

in the two first cases ,adhesiolysis may be considered if the restoration of « normal » anatomy is expected thus leading to a natural conception avoiding IVF or when access to the ovaries seems very difficult for ovum pick-up. This last situation is in fact quite rare.

In case of endometriosis, every case has to be discussed since endometriosis gives pain and infertility and also because surgery is a difficult one which a complication rate which is noticeable.

Also endometriosis is a progressive disease and if IVF is done prior to surgery and is not successful then aggravation may be expected and we had in our team several cases of bowel obstruction 1 or 2 months after IVF which led to a more complex operation that it should have been before the IVF attempt.

In fact most of the endometriosis specialized surgeons have noticed that surgery is usually more complex after IVF especially due to an extent of adhesions may be due to the egg collection procedure.

Very often pain and especially dysmenorrhea is very important and therefore it is recommended to operate these patients prior to IVF (adhesiolysis in this case is the most part of the procedure).

Every case should be discussed taking in account the quality of life of the patient, the fact that after a complete surgery 40 to 50% of patients will be able to achieve a natural conception in the following 6 months, but also the reality of complications which should be carefully explain to the patient especially if a colorectal resection is expected.

In this respect a clear consent is required for the patient.

Technically it should be clearly said that laparoscopy is the gold standard, it is feasible in nearly of the cases in experienced hands, and is the best method to reduce the risk of recurrence.

Lastly we should underline that this kind of surgery is quite challenging and requires a skillful team with, as a minimum, 2 laparoscopic surgeons gynaecologic and colorectal.

BIOMARKERS IN THE ART: CAN THEY MAKE A DIFFERENCE?"

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The importance of biomarkers in health management has long been recognised as a key factor in improving diagnostic accuracy and treatment efficacy along with achieving cost effectiveness. According to the National Institutes of Health, a biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. An ideal biomarker should be able to point to a disease process for which noninvasive or early detection is of clinical benefit.

Poor utility of biomarkers may be the result of lack of education in the parties involved in clinical medicine. Individualisation in use of each biomarker is an emerging need, as there is not a single paradigm that applies in all biomarkers in general. Often, disease aspects may be highlighted by certain biomarkers, though these may not be necessarily of clinical importance. Of particular interest is the focus on optimisation of a biomarker characteristics, such as the sensitivity and specificity aspects of it. For a biomarker to be effective appropriate use demands application in well defined groups of patients.

The identification and development of a biomarker has distinct stages that involve a clinical validation process, before a new biomarker can be introduced in everyday clinical practice. A validated biomarker has been tested both in longitudinal and retrospective cohorts for consistency in its intended use and subsequently in further prospective studies, where test characteristics are being confirmed in well defined populations. However, the current state of development of biomarkers in assisted reproduction shows that the majority of biomarkers introduced by researchers and investigators will never reach clinical practice due to lack of validation studies.

The utility of biomarkers in the assessment of ovarian response has had a strong impact on prediction of treatment response and individualisation of ovarian stimulation protocols. The use of antral follicle count and of the antimullerian hormone appear to have a synergistic effect on delivering tailor-made treatment strategies, promoting cost-effectiveness by risk reduction and accurate prognosis. Further, FSH receptor gene polymorphisms have been identified that may improve more accurate dose selection in treatment protocols.

Regarding embryo viability assessment and implantation potential there has been a tremendous increase in the uptake of comprehensive chromosome screening tests, from array comparative genomic hybridisation, to quantitative real-time PCR and more recently to next generation sequencing technology. At the same time, time-lapse imaging has successfully introduced morphokinetics as time-dependent biomarkers in cell processes during early embryo development, thus rendering embryo selection a more efficient procedure.

Implantation is another area of intense biomarker research and development. To date, no single morphologic, molecular or histologic marker has proven capable of indicating endometrial receptivity. However, following recent advances in transcriptomic analysis of human endometrium, a genomic signature related to receptivity

has been obtained. This, along with diagnostic tools based on customised microarrays have resulted in the introduction of the endometrial receptivity assay test, a tool that seems to outperform traditional histologic dating of the window of implantation. Early pregnancy may not progress in a normal way, either ending in miscarriage, ectopic pregnancy or pregnancy of unknown location. A number of biomarkers have been explored, either as individual, or multiple markers to test for the prediction of early pregnancy complications.

Moreover, cell-free fetal DNA in maternal serum can now be used as a valid biomarker in embryo ploidy assessment, thus allowing early prenatal genetic diagnosis in a non-invasive manner.

SESSION III

STRESS AND REPRODUCTION

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Abstract

Stress is the state of threatened (or perceived threatened) Homeostasis. In the CNS, the Stress system includes the Corticotropin-releasing hormone (CRH) system and the *Locus caeruleus* (LC)-norepinephrine (NE)/autonomic (sympathetic) systems. In the periphery the Stress system includes the Hypothalamic-Pituitary-Adrenal (HPA) axis and the Autonomic (sympathetic) systems. Homeostatic mediators include Hormones, Neurotransmitters, Cytokines and Growth Factors. Direct effects of Stress on the female reproductive system include Hypothalamic Amenorrhea, Abortion, Premature Labor, Perinatal Death and Fetal Restriction (IUGR). Chronic effects of stress include Obesity, Metabolic Syndrome and Polycystic Ovarian Syndrome (PCOS).

The activated HPA axis exerts inhibitory effects on the female reproductive system by suppressing the Hypothalamic-Pituitary-Gonadal (HPG) axis at the hypothalamic, pituitary, ovarian, and uterine level. Peripheral CRH promotes decidualization, blastocyst implantation and early maternal tolerance. At the same time, CRH controls fetoplacental circulation and induces fetal adrenal steroidogenesis. On the other hand, pathophysiologic roles of peripheral CRH include failed or abnormal implantation, shallow trophoblast invasion, preeclampsia, IUGR and premature or delayed labor.

WHAT IS THE OPTIMAL APPROACH FOR OVULATION INDUCTION IN PCOS PATIENTS?

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Ovulation induction provides the means for the treatment of anovulatory infertility. The aim is to stimulate single follicle maturation leading to mono-ovulation. This will reduce the rate of complications, including multiple pregnancies and the ovarian hyperstimulation syndrome. For patients with hypogonadotrophic-hypogonadism, the treatment involves both FSH and LH, while hCG is injected for follicle rupture. However, in the polycystic ovary syndrome (PCOS), the first treatment choice is clomiphene citrate. With

this drug, in properly selected patients, the cumulative pregnancy rate approaches that in normal women. Recent studies have demonstrated that letrozole, an aromatase inhibitor, can equally to clomiphene or even more successfully than clomiphene be used as first-line approach in naïve patients with PCOS. Although no difference in the rate of congenital anomalies was found between letrozole and clomiphene, aromatase inhibitors are still considered an "off-label" treatment. Low-dose protocols of FSH are the second-line treatment, inducing mono-follicular development and mono-ovulation in about 70% of the cycles. Laparoscopic ovarian drilling can be an alternative to gonadotrophins but not a first-treatment choice in clomiphene resistant patients. Although in obese women with PCOS, weight loss and exercise are recommended, pharmaceutical treatment may be necessary from the beginning. Finally, insulin sensitizers are not considered now-a-days ovulation inducing agents.

THE BEST OPTIONS FOR THE TREATMENT OF INFERTILITY IN WOMEN WITH PCOS: A PRACTICAL REVIEW

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Introduction The recognition of the controversies surrounding the treatment of PCOS led to a second international workshop endorsed by ESHRE and ASRM, held in Thessaloniki, Greece in 2007, to address the therapeutic challenges raised in women with infertility and PCOS. Evaluation of women with presumed PCOS desiring pregnancy should exclude any other health issues in the woman or infertility problems in the couple. **Lifestyle modifications.** Before any intervention is initiated, preconceptional counselling should be provided emphasizing the importance of life style, especially weight reduction and exercise in overweight women, smoking and alcohol consumption. Weight loss is recommended as first line therapy in obese women with PCOS seeking pregnancy. Multiple observational studies have noted that weight loss is associated with improved spontaneous ovulation rates in women with PCOS, while pregnancies have been reported after losing as little as 5% of initial body weight. **Clomiphene citrate.** Clomiphene citrate (CC) remains the treatment of first choice for induction of ovulation in anovulatory women with PCOS. Cost of medication is low, the oral route of administration is patient friendly, there are relatively few adverse effects, little ovarian response monitoring is required and abundant clinical data are available regarding safety of the drug. The main factors that predict outcome of treatment are obesity, hyperandrogenemia and age. Ovarian volume and menstrual status are additional factors that help to predict responsiveness to CC. There is now clear evidence that the addition of metformin or dexamethasone to CC as primary therapy for induction of ovulation has no beneficial effect. Tamoxifen appears to be as effective as CC for induction of ovulation but is not licensed for that purpose. Initial preliminary studies suggest that letrozole appears to be as effective as CC for induction of ovulation but the drug is currently not approved for treatment of infertility. **Insulin sensitizing agents.** In women with PCOS, metformin appears to lower the fasting insulin level, but does not appear to result in consistent significant changes in BMI or waist-to-hip ratio. Although oligomenorrhea improves in some women with PCOS (one extra ovulation every five woman-months), significant numbers remain anovulatory and at risk for menorrhagia and endometrial hyperplasia. In women with PCOS and a BMI < 32 kg/m there is not enough evidence to establish a difference between metformin and CC in terms of ovulation, pregnancy, live birth, miscarriage and multiple pregnancy rates. **Gonadotrophins and GnRH-analogues.** The significantly

high hyperstimulation rate, the associated risk of multiple pregnancies and the additional inconvenience and cost of concomitant GnRH agonist administration, in the absence of documented increases in pregnancy success, do not justify the routine use of GnRH agonists during ovulation induction with gonadotrophins in PCOS patients. **Laparoscopic Ovarian Surgery.** The main indication for performing Laparoscopic Ovarian Surgery (LOS) is CC resistance in women with anovulatory PCOS. Other indications include: patients who persistently hypersecrete LH, anovulatory women with PCOS who need laparoscopic assessment of their pelvis or who live too far away from the hospital for the intensive monitoring required during gonadotrophin therapy. In approximately 50% of LOS-treated women, adjuvant therapy will be required. **Assisted Reproduction Techniques.** After failure of weight reduction, anti-oestrogen therapy or LOS, it may be argued that induction of ovulation with exogenous gonadotrophin therapy should be omitted and replaced by ovarian stimulation and IVF. By utilizing IVF with single embryo transfer, the risk of multiple pregnancies is markedly reduced. In PCOS patients who do have associated pathologies, IVF is indicated, such as in case of tubal damage, severe endometriosis, pre-implantation genetic diagnosis and male factor infertility.

SESSION IV

IS DOUBLE EMBRYO TRANSFER (DET) BOUND TO IMPROVE OUTCOMES? A PHILOSOPHICAL AND PHYSIOLOGICAL QUESTION

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The early years of ART were marked by 'natural cycle' IVF and single embryo transfer (SET) was the norm. The introduction of gonadotrophin stimulation led to the production of multiple embryos in a single cycle and, especially as embryo freezing was perceived to be ineffective and possibly hazardous, it became commonplace for 3, 4 or more embryos to be replaced. There was a widespread belief that each individual embryo had a 'chance' of implanting and that the summation of these 'chances' would result in an increased chance of a pregnancy occurring.

The terrible toll of mid-trimester miscarriages and the delivery of extremely premature infants with high rates of morbidity and mortality and the maternal consequences of PET and GDM led to a recognition that multiple gestations should be avoided if possible and serial single embryo transfers, supported by extended culture to Blastocyst and cryopreservation by vitrification was adopted by many countries, with Scandinavia leading the way. In the UK, clinics are expected to follow an Elective Single Embryo Transfer policy (eSET) and are sanctioned if their multiple rate exceeds 10%. In some countries, it is actually illegal to transfer more than one embryo irrespective of the maternal age or the quality of the embryos.

However, our desire to avoid twins on grounds of neonatal and paediatric risk is not shared by many of our patients. Their interpretation of the statistics is that a DET will at least increase their chance of achieving a pregnancy and they regard the prospect of twins as a bonus! Demographic changes which reflect the tendency of couples to delay childbearing and hence needing to resort to ART, and the consistent finding that couples planning to become parents desire generally to have two children, may explain the prevalence of DET.

In this paper I will present the data from our clinic showing the evolution of the strategy to maximize live birth rates, while minimising prematurity and disability. I will ex-

plore the issues of patient autonomy and medical paternalism and address the complex statistical models that compare cumulative outcomes from eSET and DET across different patient populations. I will also discuss the latest research on embryo/epithelium crosstalk and its impact on implantation and present data from our clinic that suggests that transferring two embryos, where one is of inferior quality, may actually reduce the prospects for pregnancy.

SHOULD PGS BE OFFERED TO ALL IVF PATIENTS?

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The rate of PGD cycles undertaken to conduct embryo aneuploidy screening rather than monogenic disease diagnosis sharply increased in the last decade and such a trend is going to keep increasing in the next future. The rationale underlying PGS resides in the influence of aneuploidies in human reproduction. They have an incidence in newborns around 0.3% and are mainly represented by chromosome 13, 18 and 21 trisomies and sex chromosome impairments, however this rate increases in the stages upstream birth, as also the number of chromosomes involved does. In particular it peaks in the oocytes. This implies that a gradual arrest of aneuploid embryos takes place along preimplantation development and that there is a substantial influence of female meiosis upon embryonic aneuploidies. In fact the collapse of female fertility with ageing is reflected by both an increase in embryo aneuploidy rate and, since they are strongly related, in miscarriage rate. Oogenesis is responsible for such a phenomenon due to the block of embryo development during late prophase of meiosis I for decades up to recruitment, the asymmetric division, and the rapidity of Meiosis II soon after fertilization, all mechanisms impacted by senescence thus compromising correct chromosomal segregation. Standing that the main risks related with embryo aneuploidies are represented by implantation failure and miscarriage, the indications to the treatment are listed as advance maternal age (AMA), Recurrent Implantation Failure (RIF) and Recurrent Pregnancy Loss (RPL). The criteria to include a patient within these categories are still controversial and object of an international consensus that needs to be already built. However, at the moment a woman is considered to be AMA from 35 years of age onwards, RIF when she underwent at least 3 ETs in previous IVF cycles without conceiving, and RPL when she had to face at least 3 previous miscarriages. The benefits deriving from undergoing a PGS cycle deal with a higher efficiency of each single IVF treatment, since it aims at increasing the pregnancy rate per ET, meanwhile decreasing the miscarriage rate and the time invested by a patient to become pregnant, and this in turn translates in a higher cost-effectiveness. These outcomes are especially important for old patients spending their last chances of pregnancy, that from both psychological and logistical reasons need to avoid the useless transfer of aneuploid embryos potentially exposing them to high risks. However PGS can also apply to young women since still a baseline production of 30% of aneuploid blastocysts exists also in patients before the age of 35, thus highlighting that the whole biological process is far from being faultless at any age. In conclusion, the patients should be thoroughly informed about the pros and cons of undergoing a PGS cycle, and sign a proper informed consent. It should be clear that PGS is not aiming at an increase in the efficacy of IVF, since it is intrinsic to each couple possibility to conceive, but it definitely improves its efficiency in any patient population, as reported by the published randomized controlled trials based on blastocyst stage biopsy associated with Comprehensive Chromosome Screening (CCS) techniques, the ideal strategy to perform it.

GnRH AGONIST PROTOCOL

Konstantinos Sfakianoudis

Reproductive Gynaecologist

KING IS DEAD. LONG LIVE THE KING!!

Is this true for agonists? Is the king truly dead or is still alive?

Are agonists useless in the treatment of infertile patients?

Initial reports accused the antagonists of lack of efficiency in comparison to the agonists although this initial comparison probably misjudged the former because of the long learning curve of their use.

Nowadays, it is beyond any reasonable doubt that both agents share equal or similar efficiency globally in the treatment of infertile patients.

Questions rise concerning the efficacy of each agent in certain patient categories like those with history of endometriosis, poor responders and obese women and these are going to be analyzed during my lecture.

On the other hand, antagonists seem to be safer concerning the risk of OHSS but appropriate selection and monitoring of patients undergoing GnRh-agonist protocol seems to minimize the risk of severe OHSS syndrome.

GnRh-agonist remain the "old loyal companion" of any IVF specialist which still preserves its charming qualities against the "young seducer" antagonist...

KEY NOTE LECTURE

THE EVIDENCE FOR IUI VERSUS INTERCOURSE OR IVF

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In case of mild male infertility, it is not always clear whether expectant management ± hormonal stimulation, IUI or IVF is to be chosen. The duration of infertility and the woman's age are important in determining the preferred policy. Although IVF leads to the highest pregnancy rate/cycle, also time and cost have to be taken into account in any equation. A 2007 Cochrane review of 8 large trials could not conclude that IUI with or without hormonal stimulation led to a higher pregnancy rate per couple than timed intercourse. However, some of the trials showed better pregnancy rates per cycle for IUI than for intercourse. The 2009 IUI Capri workshop group concluded that IUI in stimulated cycles was effective only in patients with more than 3 years duration of infertility. Although IUI treatment is cheaper and less demanding on the patient, IVF is the most effective treatment. More management trials are needed to evaluate the order of treatment and overall effectiveness of treatment strategies. Data from our own group show that the age of the woman is crucial in comparing IUI versus IVF. In women over 38 years of age 3 cycles of IUI is more effective than 1 cycle of IVF, whereas under 38 it is the opposite. In conclusion, the place of IUI in the treatment of mild male infertility is still under debate.

SONOGRAPHY IN HUMAN REPRODUCTION. NEW METHODS FOR EVALUATION OF INFERTILE PATIENTS AND EARLY PREGNANCY

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During the past three decades, the managing of infertility and very early pregnancy has been substantially based on the morphometric criteria acquired using ultrasonography, endoscopy and other imaging tools, as well as measuring hCG level in maternal blood.

Effective evaluation of the clinical relevance, prevalence, and therapeutic outcomes of different morphological tools was hindered by the subjective interpretation of the original data. There was no international or interdisciplinary agreement on their application.

However, by time three-dimensional (3D) and (4D) ultrasonography has been found to be a highly accurate and reliable supplementary method.

A baseline ultrasound assessment of the pelvis in subfertile women is performed to screen for any pelvic pathologies that are known to have a negative effect on fertility and early pregnancy and also to predict ovarian reserve and endometrial receptivity. Furthermore ultrasonography is used on a daily basis in all fertility units to monitor the response to treatment during ovulation induction and Assisted Reproduction Treatment and to guide egg collection and embryo transfer in women undergoing IVF treatment.

The use of ultrasound has extended to subfertile men also for evaluation of testicular morphology and lower genital tract and for guiding surgical sperm retrieval.

Since the introduction of ultrasound as a medical diagnostic tool in the 1950s, there has been significant progress in the ultrasound technology. Development of high-frequency probes and refinements of ultrasound machines and associated softwares have helped to produce high-resolution images and thereby improving diagnostic capabilities.

Introduction of three-dimensional (3D) ultrasound and automated techniques in the last decade have further improved image qualities and facilitated more objective and reproducible volume measurements.

Improvement of gray scale ultrasound imaging along with Doppler technologies have been incorporated in almost all the fertility units around the world with an overall aim to improve the success of fertility treatments without compromising safety of subfertile couples. New ultrasound technology enhanced screening of different uterine and adnexal pathologies, as well as assessment of tubal and ovarian function. Additionally use of ultrasound in monitoring of treatment response, in assessing complications of fertility treatment and in guiding assisted reproduction treatment procedures.

Three-dimensional (3D) sonography of the uterus is a technique that allows reconstruction of the coronal plane, which improved evaluation of uterine disorders and their interaction to the endometrial canal. About 9% of all women with sterility are affected by uterine anomalies. Three-dimensional (3D) pelvic sonography has turned into

a problem-solving procedure in evaluation of a diversity of gynecologic disorders such as uterine anomalies, endometrial disorders, fibroids, intrauterine device (IUD) localization, adnexal masses, and tubal disorders. It should be used as a usual imaging protocol in the assessment of most of these disorders. It can add important clinical information to that obtained by two-dimensional (2D) imaging, and it can also be used selectively for assessment of adnexal masses.

3D ultrasonographic imaging of the female organs allows fast achievement of ultrasound images with the facility to present volume-rendered images of the uterus, ovaries, and adnexa. It has the ability to diminish operator reliance compared with 2D imaging because volume acquisitions should include all of the anatomic information, which can later be reviewed and manipulated by a different operator in a range of planes. Every preferred plane can be achieved from the volume of data that is acquired, stored, and reformatted. Volumetric imaging has the potential to make better patient management. It needs selective estimation of the acquired volume and may be restricted by accessibility to best possible scan planes for image acquisition.

In the assessment of the uterus, the most practical plane that can be acquired with 3D transvaginal sonography (TVS) is the coronal view of the uterus and adnexa. This plane cannot normally be acquired by typical 2D acquisitions. The outline and inner contour can be rebuilt to show the shape of the uterus and endometrium, which contains the fundal form and uterine cornua as well as the contiguity of adnexal disorders concerning the fallopian tube. These images can be used to better become aware of uterine disarrays, as well as the assessment of uterine anomalies, presence and place of endometrial polyps and uterine leiomyomas, IUD positioning, and assessment of adnexal or endometrial masses. The coronal plane could also be used to verify the contiguity of adnexal structures that correspond to the fallopian tube. In contrast, in the assessment of the pelvic floor, the most functional view is the axial plane, which cannot be acquired using 2D imaging but can be reconstructed by means of 3D volume handling. These 3D-rendered images may also permit the patient and the ordering physicians to better comprehend the imaging findings and assist with intraoperative planning. Other most important contributions of 3D imaging consist of Doppler evaluation within 3D volumes, better anatomic evaluation of the pelvic organs, and more precise volume measurements to better assess therapy. Vessels and volume of flow can be localized inside an area of interest. Volume measurements can be completed from the original data set. The volume can as well be analyzed with power Doppler. 2D imaging depends on the operator to find suitable images and can overlook important findings or anatomy. Volume imaging can be reviewed at a later time, even if it was not originally perceived by the primary operator or if the patient is no longer available. The images can be evaluated and discussed afterward. 2D sonography has restricted illustration of the anatomy in the coronal plane. 3D ultrasound allows the evaluation of the coronal plane, which is important in assessing the external form, uterine anomalies, evaluation of uterine polyps or leiomyomas, and assessment of IUD placement. Exact anatomic relationships can also be reconstructed and recorded.

SUMMARY

3D sonography considerably expand on the diagnostic ability of 2D sonography of the pelvic organs. It is a problem-solving technique in the assessment of a range of gynecologic disorders concerning the uterus, adnexa, and pelvic floor. It allows an precise illustration of the uterine cavity and delineate of the uterus in the coronal plane, which is tricky to visualize on 2D imaging. 3D sonography is less expensive, is

convenient, and does not have the risk of radiation or potential nephrotoxicity from contrast that other imaging modalities have. It is a cost-effective tool to assess the pelvic organs.

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REPRODUCIBILITY OF ENDOMETRIUM MEASUREMENTS IN ART PATIENTS

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Abstract

Regarding noninvasive investigation of endometrial receptivity, the advantage of vaginal ultrasound for monitoring in assisted reproduction is to visualize and accurately follow endometrial development throughout the menstrual cycle.

Although it is now standard procedure to measure endometrial thickness and pattern during ultrasound monitoring for controlled ovarian stimulation the relationship and influence of sonographic endometrial thickness and endometrial pattern to pregnancy is still under debate. When the endometrium thickness measured by ultrasound is < 7mm it is the functional layer which is thin or absent. In such condition the implanting embryo would be much closer to the spiral arteries and the higher vascularity and oxygen concentration of the basal endometrium.

Ultrasound measurement of uterine contractions and visualization of vascular network and blood flow measurements were introduced as diagnostic tool for investigation of implantation failure after ET. High degree of endometrial perfusion illustrated by both techniques on the day of embryo transfer may indicate a more favorable endometrial milieu for successful implantation.

In infertile women uterine artery pulsatility index measured during the midluteal phase of natural cycles, correlates inversely with endometrial thickness, suggesting a direct effect of uterine perfusion on the endometrial growth. Furthermore, pulsatility index correlates directly with the age of the patients, suggesting a detrimental effect of age on uterine perfusion.

No difference was found in the predictive value of scoring systems analyzing endometrial thickness and volume, endometrial morphology and sub-endometrial perfusion by color Doppler and 3D power Doppler ultrasonography.

2D AND 3D EVALUATION OF THE UTERINE CAVITY- IS IT ENOUGH? THE ROLE OF HYSTEROSCOPY

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Transvaginal sonography is most important tool for intrauterine pathology diagnosis in infertility treatment, but is it enough to make complete diagnosis before we proceed to IVF? Even the majority of pathology related to uterine cavity, endometrial tissue and muscular wall could be recognised, accuracy of TVS still remain questionable for some diagnosis, requiring additional diagnostic techniques like hysteroscopy, laparoscopy or MRI. Never the less, we have to keep in mind fact that ultrasonography is diagnostic tool dependent of operator skill, patients characteristic, menstrual period timing and equipment quality. One of examples is incidence in Mulerian tract anomalies(MTA), varying from 0,06-38%(in infertile population from 3-11 %), depending of screened population characteristics, number and accuracy of different diagnostic procedures applied to certain group of patients (TVS only, or plus 3D, hysteroscopy, laparoscopy, MRI, SIS, HSG).

Optimal diagnostic tests for MTA are MRI and hysteroscopy (Saravelos 2008) or 3D

TVS, laparoscopy in conjunction with hysteroscopy (or HSG, SIS or MRI), suboptimal diagnostic tests are 2D TVS, hysteroscopy and HSG (Chan,2011) but in both cases the prevalence of MTA was the same. TVS provide accuracy in 90%, sensitivity 75-100%, specificity up to 95%. In patients with surgically proven diagnosis, accuracy of imaging in MTA classification was: MRI 100%, 2D-TV 92%, HSG 20%, but to determine who need operative correction there was no difference among MRI and 2D-TV – 100% (Pellerito, 1992). More reliable is 3D TVS because proper external uterine contour and volume with 93% sensitivity, 100% specificity and PPV 100%. Still, concordance with endoscopy is 96%, and very high with MRI, but MRI is more accurate in exploration of uterine lower part and 3D should be complemented by gynaecological examination of cervical part of uterus. Two techniques are comparable in accuracy and efficacy, and 3D is less demanding. Still, for some uterine anomalies additional diagnostic methods a part of 3D US are necessary.

In endometrial pathology like polyps, Asherman syndrome (complete or partial), endometrial carcinoma, endometrial hyperplasia and degenerative changes like endometritis and mycopolyposis, mostly additional diagnostic procedure like hysteroscopy is needed. The last two mentioned is not possible to detect by US, only by hysteroscopy. Accuracy in polyps diagnosis is: poor specificity for 2D TVS – 69%, SIS more accurate, increase specificity to 94%, for 3D specificity 88,8%, combined with SIS – 100%. Many studies compared ultrasonography and hysteroscopy, and mainly in results unrecognized intrauterine pathology was found by hysteroscopy (up to 40% normal ultrasound exam was denied by hysteroscopy diagnosed and corrected pathology). On the other hand, TROPHY study in conclusion finds no significant difference in IVF success with or without hysteroscopy before IVF. Still, results were different comparing centers in some success was higher with hysteroscopy.

In conclusion 2 D US should be initial method for screening, addition of 3D mainly can provide diagnosis, but combined with SIS could increase accuracy. In certain cases some additional test must be used before we proceed to IVF, even sonography is powerful tool. But it is just like on of our senses, not the only one is enough to make complete picture.

KEY NOTE LECTURE

THE ROLE OF SPERM CHROMATIN STRUCTURE IN COUPLE'S INFERTILITY AND ITS SENSITIVITY TO DIETARY MANIPULATION

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There is good consensus on the concept that the oxidative damage to gametes represents a relevant clinical issue. However, the latest Cochrane review[1] concluded for low quality evidence that antioxidant supplementation in subfertile males may improve live birth rates and clinical pregnancy rates for couples attending fertility clinics. The same considerations apply to female infertility where clinical data in support are even weaker[2]. The above discrepancy is in part explained by the aggressiveness of direct antioxidants, forcing the cellular environment to the redox state, in front of the delicate metabolism of the gametes that necessitate a perfect oxy-redox balance. Strong direct antioxidants may cause an excessive removal of oxygen free radicals essential for the regulation of several sperm functions: This may

negatively affect capacitation and the acrosome reaction[3] and in case induce a "reductive stress" as a rebound effect [4]. This was confirmed by the worsening of the sperm nuclear condensation, a very negative outcome, proportionally mirroring any improvement of the DNA fragmentation when strong antioxidants (Vit. C + Vit E + Beta-carotene + Zinc + Selenium) were administered [5].

However, oxidative molecular damages occur in all cells and may get repaired: Spermatids, oocytes and zygotes possess powerful, although finite, DNA repair capacity[6]. On the other side, compensative or repairing mechanisms capable to put remedy to damages beyond simple molecular oxidations, i.e. to the chromatin structure, have not been yet described. It is nowadays evident that, besides the genes, gametes provide a structural framework that includes molecular regulatory factors required for proper embryonic development[7]. The oxidative aggression may affect the chromatin structure and the genomic activation at least in two relevant manners: In sperms by affecting the protamin content[8]; In both sperms cells and oocytes, oxidation of either the methyl-cytosine (forming OH-mC) or of guanosine (to form 8-oxo-G) within otherwise properly methylated CpG islands causes loss of the inhibition of the binding of the transcription factors, which has been proposed as a mechanism for the loss of genomic regulation following environmental damage[9]. Chromatin condensation is essential for a mature sperm and also occurs during oocyte maturation. This process is strongly dependent on the deposition of methyl marks on the chromosomes and requires full efficiency of the 1 carbon cycle (1CC) pathway ensuring active methyl groups for transmethylation. The same methyl groups are in turn essential to activate the intracellular antioxidant defences (GSH production) within a complex although perfect regulatory balance allowing the cell to activate the defences only if the requirements for growth and differentiation are satisfied. Accordingly, it was postulated that a robust nutritional support to the 1CC could result in both improved DNA methylation, sustaining gametes maturation, and activation of the endogenous antioxidant system, configuring an indirect antioxidant activity devoid of any risk of "reductive stress".

A nutritional supplement containing all the substances necessary to support the 1CC (Vit. B2, B3, B9, B12 and zinc) and the GSH production (cysteine donor, Vit. B6 and zinc) was formulated and clinically tested[10-12]. The supplement also contained betalain and quercetin of vegetal origin to protect membrane lipids and small amounts of Vit. E as a stabilizer (CondensylTM). This nutritional intervention has been tested in male[10-12] and female[12] partners in ARTresistant couples in preparation of a new ART attempt. These studies included couples with at least 2 ART failures and with a male partner sperm DNA fragmentation index (DFI - Measure of oxidative molecular damage, TUNEL) and/or a sperm nuclear decondensation index (SDI - Measure of integrity of chromatin tertiary structure, aniline blue staining) > 20% irrespective of the other sperm parameters. A 4 month nutritional support was prescribed.

A total of 84 patients fulfilled the entry criteria of the first, non comparative, study[10], in 28 cases (33%) there was an associated female factor. For the first time ever both the sperm indexes significantly improved (DFI from 29.7% to 23.1%, $p < 0.001$; SDI from 40.1% to 36.3%, $p < 0.001$). In all 40 clinical pregnancies were achieved, 33 of them ending with a live birth. Eighteen couples (21%) experienced a spontaneous pregnancy during the treatment, all of them ending with a live birth. The remaining 66 couples underwent a new ART attempt further resulting in 22 clinical pregnancies and in 15 live births. The overall clinical pregnancy rate (CPR) and live birth rate (LBR) were 47.6% and 39.3% respectively. The pregnancies were strongly related to the improvement of the decondensation index (Table 1).

The intervention was then tested in comparison with a non-treatment group using the same supplement[11] or a similar one including also small amounts of natural direct antioxidants named ProcreliaTM[12]. Again, both the DFI and the SDI significantly decreased in the male treatment groups whereas they did not change in their controls. The pregnancy rates were significantly higher in the treatment groups in all study arms with a high rate of pregnancies occurring spontaneously, i.e. before the planned ART cycle. The pregnancy outcomes of the male partners and their controls[11,12] and of the female partners and their controls[12] are summarised in Table 2.

Taken together these data strongly support the idea that a tailored nutritional intervention in support of the ICC and of GSH synthesis may have a fundamental impact on the reproductive prognosis of couples resistant to ART cycles.

The high rate of spontaneous pregnancies, absent in control groups, was surprising considering the population and indicates the occurrence of a significant rate of ART-resistant couples whose infertility seems strongly linked to metabolic imbalances. Accordingly, an adequate nutritional care offered since the first referral might decrease the need for repeated ART cycles and may also help to increase the chances of IUI.

Table 1 DFI and SDI response according to clinical pregnancies, mean values, Mann-Whitney test[10]

Groups	n (%)	DFI				SDI			
		Pre	Post	Diff. %	p	Pre	Post	Diff. %	p
Any pregnancy									
YES	40 (47.6)	29.4%	20.1%	-9.3%	0.168	40.6%	29.3%	-11.3%	0.000
NO	44 (52.4)	30.1%	25.9%	-4.2%		39.6%	42.6%	3.0%	
Spontaneous pregnancy									
YES	18 (21.5)	23.2%	18.4%	-4.8%	0.571	44.8%	29.8%	-15.0%	0.000
NO	66 (78.5)	31.5%	24.4%	-7.2%		38.8%	38.0%	-0.7%	
ART pregnancy									
YES	22 (33)	34.4%	21.4%	-13.0%	0.046	37.2%	29.0%	-8.2%	0.001
NO	44 (67)	30.1%	25.9%	-4.2%		39.6%	42.6%	3.0%	

Table 2 Comparative studies[11,12]: pregnancies and deliveries, mean values, Chi square test

	N of pts	Pregnancies, n (%)		Deliveries	p
		All	Spontaneous		
Only men treated, female partner "normal"[11]					
Treated	69	35 (50.7%)	10 (29%)	29 (42%)	0.003
Controls	83	23 (27.4%)	0 (0%)	18 (21%)	
Only men treated, female partner "normal"[12]					
Treated	95	49 (56%)	8 (16%)	45 (47%)	0.001
Controls	84	23 (27%)	0 (0%)	18 (21%)	
Only women treated, male partner "normal"[12]					
Treated	100	45 (45%)	30 (67%)	40 (40%)	0.0001
Controls	73	10 (14%)	0 (0%)	8 (10.9%)	

Finally, the strong relation between the occurrence of a pregnancy and the improvement of the sperm nuclear condensation in the male partner (Table 1) is a definite proof of the main role of chromatin structure in gametes reproductive competence. This understanding leads to revisions of the current diagnostic and clin-

ical approaches. Based on the negative effects of direct antioxidants on sperm nuclear condensation their indiscriminate use should be avoided. These treatments should be prescribed only to patient with a confirmed damage under strict medical control. On the other side, nutritional supports based on indirect antioxidants, e.g. Condensyl, did not exert any counter effect and, opposite, improved also the sperm nuclear decondensation while significantly reducing DNA fragmentation. These treatments could be hence offered before seeking pregnancy to a larger population and without fixed limits of duration.

In conclusion, a nutritional support with indirect antioxidants (Condensyl™) improves the clinical outcomes in couples infertility due to a male factor and may work also in female infertility and in support to natural reproduction. The strong correlation between the pregnancies and the SDI decrease in males supports a main role of the chromatin architecture in treatment response as well as in couples infertility. Further studies are needed to clarify the molecular and structural basis of these effects and the best cost-effective diagnostic algorithm.

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WHEN IS MYOMECTOMY INDICATED IN ART PATIENTS?**Vasilios Tanos MD PhD, Prof in Obstetrics and Gynaecology***St'Georges Medical School, Nicosia University and Aretaeio Hospital, Nicosia, Cyprus*

Myomas present the most common benign tumors in women of reproductive age with a cumulative risk by the age of 40 nearly 50%. During infertility treatments and especially before IVF the presence of intramural fibroids, brings the debate if it is better to operate or not such cases prior to ART. The main concerns are interference with implantation, dysfunctional contractility and poor regional blood flow resulting in focal endometrial attenuation or ulceration. The Ultrasonographic detection is easy and cost effective while 4D US provides even more accurate diagnosis of size and precise location of the myoma in relation to the endometrial cavity and myometrium. MRI is also extremely useful in cases of multiple fibroids with complex morphology and especially helpful to identify myomas with necrosis and the high risk for sarcomatous changes. The subserous fibroids usually do not disturb fertility except those located close to the cornua compressing the tubal endolumen or affect tubal contractility. The submucous fibroids usually cause chronic endometrial inflammation and di-synchronize endometrial contractility while those protruding in the endometrial cavity act as IUD. The debate about myomectomy prior to ART focus on the intramural myomas. The size of an intramural fibroid is considered important, especially those over 3-4cm and few studies showed a considerable increase in PR after myomectomy although the endometrial cavity was normal. When the size of an intramural fibroid is over 7cm usually the cavity is distorted and hysteroscopy is the gold standard procedure to evaluate an endometrial cavity abnormality. A clinical indication for myomectomy might also be an IM fibroid after 2 failures of IVF considering that other infertility risk factors are absent. Smaller size intramural myomata usually are considered not harmful for implantation and the destruction to the uterus by the operation might be more risky. Intramural myomata located in the fundal area might also be more detrimental to implantation than other locations even those <3cm, however this fact remains to be evaluated. When the size of the fibroids are >4cm and especially in the fundal area we might consider myomectomy prior to ART taking in consideration patient's age, embryo quality and endometrial thickness. Operative laparoscopy is the preferable technique of treatment although hysteroscopic surgery under US guidance is also possible in very experienced hands. Removal of an intramural myoma solely to improve or to treat infertility is controversial because benefits are uncertain, mainly due to lack of RCTs. Data suggests that serious consideration and skepticism regarding the value of intramural myomectomy with a normal endometrial cavity prior to IVF is justified. Once myoma, accompany a pregnancy the obstetrical risks should also be taken in consideration since the risk of miscarriage and post partum hemorrhage are increased. The management of intramural myoma in infertile women must be highly individualized and consideration given to relative risks benefits and consequences of different surgical treatments. Age, ovarian reserve, reproductive history, duration of infertility, the size, number and location of myoma are parameters of concern leading to final decision.

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