

Endometrium from Physiology to Pathologies Highlights

***Bologna (Italy), February 23-25, 2017
Highlights***

Introduction



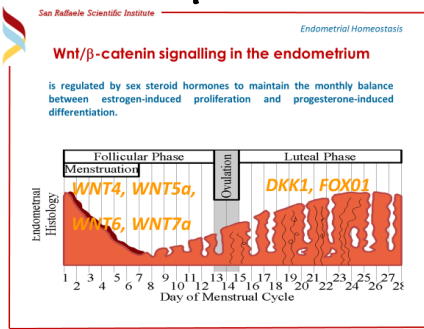
Prof. Seracchioli, chairman of the symposium, opened the congress, by highlighting the high scientific level of this congress focused on endometrium and its main mechanisms of control leading to new pharmaceutical compounds as a very important challenge for gynaecologists. Many top researchers in endometrium physiology and pathology, coming from all the world attended this symposium together with young physicians

and gynaecologists. This congress represented a very unique occasion for a full update on Endometrium from physiology to pathology and the related pharmacological and surgical treatment.

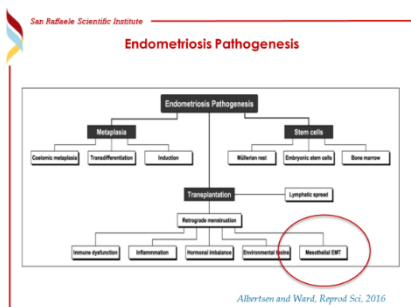
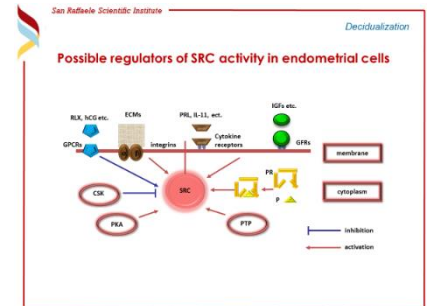
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Stromal-epithelial interactions, mechanisms of migration and invasion



about the genomic and non-genomic estrogen-mediated endometrial proliferation and presented very interesting data on the role played by the stromal growth factors and more in particular by Wnt/β-catenin as a mediator of the progesterone activity on the epithelium. Prof. Viganò spoke also about the main mechanisms of the epithelial transition toward the mesenchymal tissue and more in particular on the lack of β-catenin, responsible for the aberrant gene expression of progesterone dependent genes acting on epithelium. In conclusion, Prof. Viganò pointed out that the interaction between the stroma and the epithelium is critical for some endometrial functions and that the GWA studies may allow to identify genetic variants associated with endometriosis and the epithelial mesenchymal transition.



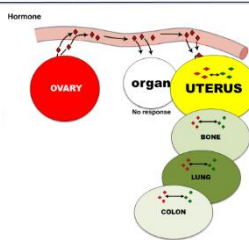
- What is the role played by β-catenin on the mechanisms leading to the epithelial mesenchymal transition?
- What are the main topics of the pathogenesis of endometriosis presented by the speaker?
- What are the two models presented by the speaker about the relationship between epithelium and endometrium leading to endometriosis?
- What are the main mechanisms leading to the estrogen-mediated endometrial proliferation?

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Endocrine and intracrine regulation of estrogens in the human endometrium

2. INTRACRINOLOGY



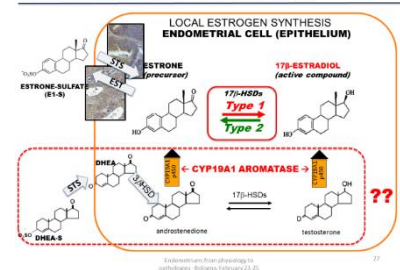
Van den Berg et al. 2012

Endocrinology from physiology to pathologies - Bologna February 22-23

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Prof. Romano from Maastricht (The Netherlands), spoke about the endocrine and the intracrine regulations of estrogens in the human endometrium. The speaker went deeper in his talk, by presenting very interesting data on intracrinology, the medical science studying the interactions between estrogens and endometrium. More in particular Prof. Romano highlighted that endometrium is not a simple container of estrogens but one of the main actors of their metabolism. In the main part of his presentation, Prof. Romano spoke about the endometrial disorders estrogen dependent, like endometriosis and endometrial cancer, by highlighting that the reaction modulating the local estrogen synthesis in the endometrial cells is controlled by the type 1 and type 2 17 β -HSDs. Prof. Romano spoke also about the androgen synthesis in endometrium controlled by CYP19A1 aromatase. Talking about treatment, the speaker presented very interesting and innovative data on novel drugs acting at two levels: the 17 β -HSDs and the aromatase enzyme. In conclusion, the speaker pointed out that it is of high importance to integrate neuroendocrinology with intracrinology for a better comprehension of all the mechanisms leading to the endocrine balance and regulation of the endometrium.

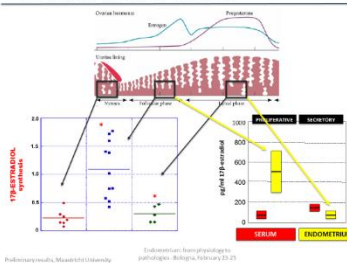
3. INTRACRINOLOGY - ENDOMETRIUM



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4. FUTURE PERSPECTIVES



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- What is the role of intracrinology in the local synthesis of steroids?
- What is the relationship between intracrinology and endometriosis?
- What is the reducing/oxidizing 17 β -HSD activity in endometrial cancer from the intracrinology view?
- What is the main function of the CYP19A1 Aromase enzyme in the endometrial cells?
- What's about the Aromatase and STS inhibitors based on the data presented by the speaker?

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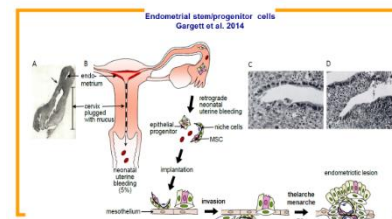
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The endometrium from the neonate to the adolescent

Neonatal menstruation		
Incidence		
	n	Incidence
Huber et al.(1974)	350	3.3%
Lévy et al. (1984)	1207	4.7%
Berić et al. (1985)	2477	3.9%

The endometrium from the neonate to the adolescent was the topic Prof. Brosens spoke about in his lecture. The speaker coming from Leuven (Belgium), started his talk, by presenting a selection of the european publications on the neonatal menstruation and on its incidence. Prof. Brosens spoke also about the adolescent endometriosis, by highlighting that babies with a birth weight below 2500 gm have an increased risk of

developing deep infiltrating endometriosis during adolescence. From the pathogenetic point of view the speaker pointed out that in these patients, during thelarche, the endometrial stem progenitor cells wake up, proliferate and establish ectopic endometrial peritoneal endometriotic lesions, under the influence of rising estrogen levels. In the last part of his talk, Prof.



Role of early menstruations in preconditioning the JZ

- Both menstruation and pregnancy are inflammatory conditions that causes a degree of physiological ischemia-perfusion tissue injury in pregnancy.
- Menstruations may serve to protect uterine tissues from hyperinflammation and oxidative stress associated with deep placentation

Brosens spoke about preeclampsia in adolescents, by presenting very interesting and recent data on the main obstetrical disorders. In conclusion, Prof. Brosens pointed out that the neonatal uterine bleeding, the dysmenorrhea and the first period of regular menstruations are the common events with a potentially great impact on the reproductive outcome in adolescents.

- What's about the delay of diagnosis of the premenarchal endometriosis based on the data presented by the speaker?
- What is the pathology-based surgery of the adolescent endometrioma presented by the speaker?
- Are early menstruations beneficial?
- Why does neonatal menstruation cause pelvic endometriosis in the adolescents?

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Menstrual physiology: implications for endometrial pathology and beyond



The implications of the menstrual physiology in case of endometrial pathology and beyond was the topic at the core of the lecture discussed by Prof. Critchley. At the beginning of her lecture the speaker, coming from Edinburgh (UK) presented very interesting data on menstrual physiology and its complexity, on progesterone and menstruation, on the role of the endometrial hypoxia, on the mechanisms of endometrial bleeding

and finally on targeting the PR for therapy. Speaking about the menstrual bleeding, Prof. Critchley pointed out that HMB is a chronic complaint that has an important impact on the quality of life of a large proportion of reproductive-age women and also presents a heavy burden in direct and indirect costs. Going deeper in her lecture, the speaker talked about the endometrial homeostasis and its complexity, by highlighting the role played by progesterone and its critical period of withdrawal. In the last part of her presentation, the speaker talked about the chronic abnormal uterine bleeding and its therapy, by presenting very interesting data on the PR ligands, their mechanisms of action and on their activity on the sex receptor expression. In conclusion, Prof. Critchley pointed out that the endometrium is a very interesting model for the study of the main physiological and pathological processes involving the human body.

- **What are the processes at the endometrial levels that impact on bleeding?**
- **What are the main mechanisms of menstrual bleeding control and endometrial repair presented by the speaker?**
- **What's about the role played by hypoxia in the tissue remodelling during menstruation?**
- **What are the repair factors expressed in the endometrium during menstruation?**

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Mechanisms of menstruation and endometrial haemostasis



The Mechanisms of menstruation and endometrial haemostasis was the topic of the lecture discussed by Prof. Bulletti. The speaker, coming from Cattolica (IT), introduced his talk by presenting very interesting data on the mechanisms of menstruation from a physiopathological point of view, by highlighting that the knowledge of these processes is critical for understanding also the diseases affecting the endometrium during the menstrual

cycle. In the main part of his presentation, Prof. Bulletti talked about two scenarios linked with the menstrual cycle: the endometrium aspects with and without any embryonal implantation. Prof. Bulletti presented very interesting data on the endometrial growth regulation in physiological state and in presence of adenocarcinoma. In the second part of his lecture the speaker talked about the vascular processes leading to the alterations of the vascular integrity and the loss of tissue and its disruption due to the metalloproteins activity. Finally, Prof. Bulletti spoke about the mechanisms of haemostasis.

- **What are the main endometrium tissue transformations during the proliferative and the secretive phases?**
- **What's about the appearance of pinepodes during the implantation phase?**
- **What is the role played by the endometrium growth factors in the proliferation of the stromal cells?**
- **What's about Angiogenesis in the menstrual cycle based on the data presented by the speaker?**
- **What is the main activity of the metalloproteins in the matrix?**

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Adolescent endometrial bleeding

Differential diagnosis for abnormal bleeding in adolescents

Pregnancy Pathology

Implantation
Ectopic pregnancy
Threatened, spontaneous, or missed abortion
Retained products of conception

Molar pregnancy

Adolescents were 7.0 times as likely to develop CM (95% CI 3.6-8.9, p<0.001) (not partial mole).

Gockeley et al., Gynecol Oncol 2016

The adolescent endometrial bleeding was the topic of Prof. Bruni presentation. The speaker, coming from Pistoia (IT), started her lecture, by presenting data on menstrual bleeding symptoms in patients affected by different diseases like the Von Willebrand syndrome and the Polycystic Ovary syndrome, that is the first one pathology responsible for endometrial bleeding. Prof. Bruni spoke also about many infectious diseases leading to bleeding in adolescents like Celiac disease or Ehlers Danlos

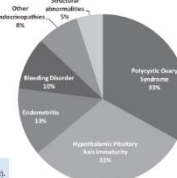
syndrome. In the second part of her lecture, Prof Bruni, talked about diagnosis, by presenting very interesting data on the assessment of the bleeding pattern, on anemia and other associated symptoms and finally on chronic illnesses due to medications. The speaker presented also data on Imaging for the

adolescent endometrial bleeding diagnosis. In the last part of her lecture, Prof. Bruni spoke about treatment, by presenting very interesting data on the heavy menstrual bleeding at menarche, other hormonal treatments like combined contraceptives, progestins and ovulation inductors. Finally, Prof. Bruni spoke about the surgical treatment of the acute menorrhagia.

Differential diagnosis for abnormal bleeding in adolescents

Endocrine

Thyroid disorders
Hyperprolactinemia
Polycystic ovarian syndrome
Adrenal disorders
Ovarian failure (?)

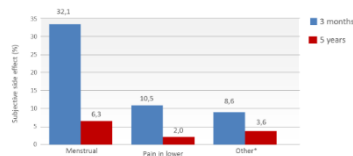


Maslyanskaya S, et al 2016

Etiology of abnormal uterine bleeding (AUB) in adolescents admitted to a children's hospital (N=102).

Subjective side effects reported at 3 months (n=1821) and after 5 years (n=736) expressed as %

LNG IUS 20 in women



* Other: acne, back pain, migraines, headache, depressed mood, nausea

1. Andersson K, et al. Contraception 1994;49:56-72.

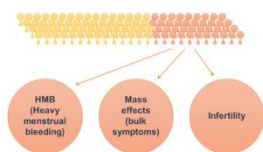
- What are the main non-surgical managements of heavy menstrual bleeding?
- What's about the LNG-IUS effectiveness from the speaker point of view?
- What are the main mechanisms of action of the LNG IUS intrauterine systems?
- What's about the efficacy of the oral progestins from the speaker point of view?
- What's about the combined contraceptives therapies in adolescent endometrial bleeding?

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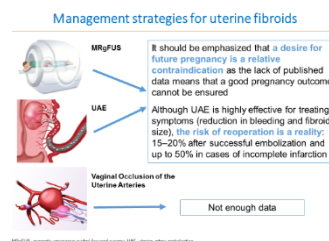
Bleeding and uterine myoma: mechanisms and therapeutic possibilities

Around 40% of women with fibroids have significant symptoms

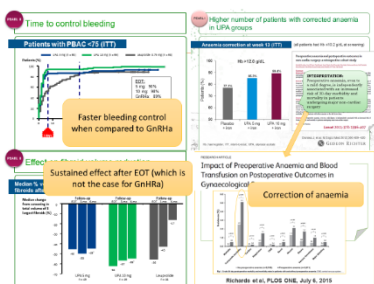


myomas, by highlighting that from a therapeutic point of view both surgical therapy and non-surgical alternatives are non-optimal and we need for new options especially when fertility maintenance is the goal. In the main part of his lecture, the speaker talked about the main characteristics of the GnRH

The mechanisms of bleeding related to the uterine myoma and their therapeutic possibilities was the topic of Prof. Donnez presentation. The speaker, coming from Brussels (Belgium), talked about the risk factors for uterine fibroma, by presenting data on the genetic factors leading to the onset of the uterine myomas. Going deeper in his lecture, Prof. Donnez spoke about the diagnosis and the management of the uterine



activators and of the SPR modulators, by highlighting that the SPRMs present a faster bleeding control, a sustained effect after EOT and finally correct the anemia. Prof. Donnez presented a huge amount of data on SPRMs long-term efficacy and safety and on the possibility to avoid or to postpone surgery or to prevent recurrence after surgery and also on the possibility to prevent occurrence in women genetically predisposed to develop myomas. In conclusion, the speaker pointed out that SPRMs are the new options for the uterine myoma treatment especially when fertility maintenance is the goal.



- What are the main factors controlling the fibroid growth?
- What are the main characteristics of the selective progesterone receptor modulators based on the data presented by the speaker?
- What are the main effect of UPA on fibroid volume reduction?
- What's about UPA safety, based on the data presented by the speaker?
- What's about the long-term nonsurgical control with UPA?

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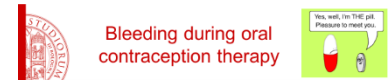
Bleeding during contraception therapy



- First months of e/p use
- Small amount of blood (spotting)
- Its features depend on
 - type, dosage, lasting of the progestagen
 - e/p balance
 - Endogenous hormones level
 - Individual answer
 - Forgotten pills/smoke/medications

these patients by highlighting the importance to collect a very useful and complete clinical history. Talking about instrumental diagnosis, the speaker pointed out that it is not always required with the exception of women over 45 years old, with a persistent

Prof. Zannoni, coming from Bologna (IT) spoke about bleeding during contraception therapy, by presenting very interesting data on the breakthrough bleeding due to several causes like type, dosage and lasting of contraceptive therapy, endogenous hormones' level, defects in pills assumption, other medications assumption and smoking. Going deeper in her lecture, Prof. Zannoni spoke about the management of



- Higher EE dosages in COC regimens appear to provide greater endometrial stabilization and less breakthrough bleeding
Hickey M, J Fam Plan Reprod Health Care 2009
Darwish M, Reprod Sci 2014
- The flexible-extended regimen is useful to reduce unscheduled bleeding
Edelman A, Cochrane Database of Syst Rev 2014

bleeding or with no effect of the medication trial. In the main part of her lecture, Prof. Zannoni spoke about therapy by discussing on the main therapeutic options like combined hormonal contraception (CHC), Progesteron-only pill (POP) and LARC like IUS, etonogestrel implant and copper IUD. In conclusion, Prof. Zannoni pointed out that there is little evidence of the effectiveness of the treatments, but still they can work on an individual basis.

Etonogestrel Implant


	LNG IUS 20	LNG IUS 14	ENG IMPLANT
Amenorrhea	44% after 6 months 50% after 12 and 24 m	6% at year 1 12% at year 3	22% after 3 months
Unscheduled bleeding In the first 3 months	35% prolonged or frequent bleeding	59% prolonged bleeding 42% irregular bleeding 31% frequent bleeding	17.7% prolonged bleeding 6.7% frequent bleeding
Unscheduled bleeding After 1 year	4% prolonged or frequent bleeding	9% prolonged bleeding 23% irregular bleeding 8% frequent bleeding	16% prolonged bleeding 7% frequent bleeding
Discontinuation	5.9%	5%	23%

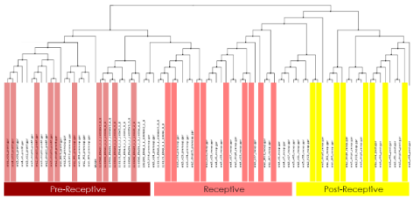
- What are the main CHC regimens presented by the speaker?
- What are the main practical rules for women with bleeding during CHC presented by the speaker?
- What's about bleeding during progesterone-only contraception?
- What are the main characteristics of the treatment for bleeding associated with LNG IUS?
- What's about the treatment for bleeding associated with ENG implant?

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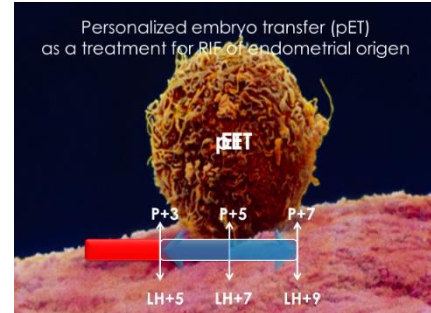
Recurrent implantation failure: the role of the endometrium

IVI |  Predictor Classifies the Molecular Receptivity Status of the Endometrium



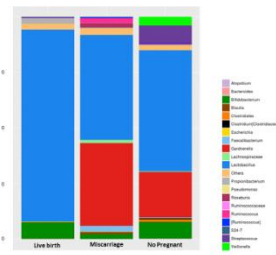
The role of endometrium in the recurrent implantation failure was the topic at the core of Prof. Pellicer presentation. The speaker, coming from Rome (IT), at the beginning of his talk, addressed the audience by highlighting that approximately only the 66% of the blastocysts implants have success and talked about the so called “puzzle of the Endometrial Factor”. In the main part of his lecture Prof Pellicer spoke about the role

of the endometrial receptivity array (ERA) and analysis (ERA-NGS), by presenting very interesting and innovative data on the ER Map as a major predictor of the molecular receptivity status of the endometrium. In the second part of his lecture, Prof. Pellicer presented data given by a clinical trial running in his clinical center, on PET, that is the personalized embryo transfer, as a treatment for the recurrent implantation failure of endometrial origin. More in particular the speaker presented the main characteristics of this study, like the inclusion/exclusion criteria, the study design and the results of the interim analysis, by highlighting that with this technique the adequate endometrial receptivity can



growth more than 14%. In the last part of his talk Prof. Pellicer presented new data on another clinical study performed by his team of research, on the endometrial microbiome, by highlighting that the low presence of lactobacillus in the endometrial microbiota is associated with poor reproductive outcomes in infertile patients.

LOW ABUNDANCE OF *Lactobacillus* IN ENDOMETRIAL MICROBIOTA IS ASSOCIATED WITH POOR REPRODUCTIVE OUTCOMES IN IVF PATIENTS



Moreno et al. Am J Obstet Gynecol 2016

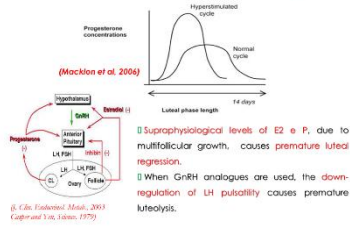
- What's about the adequate endometrial receptivity from the speaker point of view?
- What's about the puzzle of the Endometrial Factor presented by the speaker?
- What is the role of hysteroscopy for the uterine evaluation in failed ART?
- What are the main key point of the Endometrial Receptivity Array?
- What's about ER Map?
- What's about the application of the Personalized embryo transfer based on the speaker's experience?
- What's about the correlation between endometrial microbiome and recurrent implantation failure?

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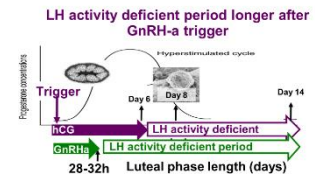
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Endometrial support for assisted reproduction cycles

Causes of LPD in stimulated cycles



The Endometrial support for assisted reproduction cycles was the topic discussed by Prof. Borini. The speaker, coming from Bologna (IT), presented very interesting data about the luteal effects of progesterone and more in particular on the causes of the luteal phase defects in natural cycles. Going deeper in his presentation, the speaker talked about the effects of the luteal phase support protocols, by presenting very interesting data given by many clinical studies running in patients with primary or secondary infertility. Prof. Borini talked about the effectiveness of LPS methods in fresh ET after HCG trigger, by highlighting that Progesterone is as effective as HCG and discussed very interesting data about the Vaginal delivery options. Finally, the speaker talked about the main treatment protocols based on the administration of 3 Progesterone versus HCG regimens. In conclusion, Prof. Borini pointed out that LPS is mandatory to overcome LH deficiency when a fresh transfer is planned.



Adapted from Prof. Humaidan
Darawad et al., 1999; Cohen et al., 1990; Kawanishi et al., 1991;
Williamson et al., 1998; Thordarson et al., 1998

Prof. Borini talked about the effectiveness of LPS methods in fresh ET after HCG trigger, by highlighting that Progesterone is as effective as HCG and discussed very interesting data about the Vaginal delivery options. Finally, the speaker talked about the main treatment protocols based on the administration of 3 Progesterone versus HCG regimens. In conclusion, Prof. Borini pointed out that LPS is mandatory to overcome LH deficiency when a fresh transfer is planned.

Evidence of impaired endometrial receptivity after ovarian stimulation for in vitro fertilization: a prospective randomized trial comparing fresh and frozen-thawed embryo transfer in normal responders

Borini F, Shapiro M, Pini R, Judd T, D'Amico M, et al. (2003) Evidence of impaired endometrial receptivity after ovarian stimulation for in vitro fertilization: a prospective randomized trial comparing fresh and frozen-thawed embryo transfer in normal responders. *Human Reproduction* 18:1061-1065.

Objective: To compare outcomes between fresh ET after ovarian stimulation and frozen-thawed ET (FET) after artificial endometrial preparation, to compare endometrial receptivity.
Design: Randomized, controlled trial.
Setting: Private fertility center.
Patients: There were 73 patients completing both frozen-thawed transfer (fresh group) and 70 patients completing FET (concomitant group). All were between 25 and 35 years of age, 45 sperm, which had 100% motility, and 3-15 oocytes retrieved.
Interventions: Randomized to fresh or frozen ET.
Main Results/Measurements: Clinical pregnancy rate per transfer.
Results: The clinical pregnancy rate per transfer was 36.7% in the fresh group and 30.7% in the FET group. The implantation rate was 78.8% and 50.7%, respectively. The ongoing pregnancy rate per transfer of 10 weeks' gestation was 38.8% and 30.9%, respectively. The cumulative risk percentage of implantation failures due to reduced endometrial receptivity in the fresh group was 44.7%.
Conclusions: The clinical pregnancy rate per transfer was significantly greater in the concomitant group than in the fresh group. These results strongly suggest impaired endometrial receptivity in fresh ET cycles after ovarian stimulation, when compared with FET cycles with artificial endometrial preparation. Impaired endometrial receptivity apparently accounted for most implantation failures in the fresh group. *Child Welfare* (London, NCT00051625) (first born) 2003;18(10):1061-1065. © 2003 by American Society for Reproductive Medicine.

- Does the type of progesterone matter in endometrial support for assisted reproduction cycles?
- What are the main vaginal delivery options presented by the speaker?
- What's about the luteal phase effect in patients undergoing NC-FET?
- What's about the preparation of endometrium for frozen embryo replacement cycles based on the data presented by the speaker?

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Blastocyst endometrium cross-talk

What else can we investigate?

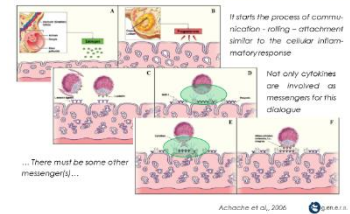


© 2014 S. Ubaldi

Prof. Ubaldi, talked about the cross-talk between blastocyst and endometrium. The speaker coming from Rome (IT), started his speech by highlighting that at least the 50% of euploid blastocysts still fail to implant and addressed the audience with these question: which parameters could further increase our predictive potential? Going deeper in his presentation, Prof. Ubaldi talked about the studies performed in the last ten years on blastocyst morphology and on time-lapse parameters of

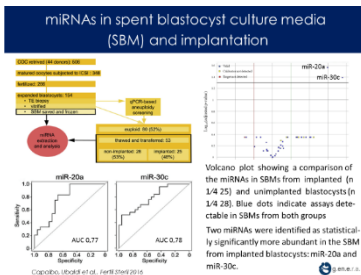
embryo evaluation, by highlighting that no conclusive results have been obtained for finding novel biomarkers of oocyte competence and embryo implantation. In the second part of his lecture Prof. Ubaldi presented very interesting and innovative data on studies performed on the endometrial receptivity and its gene expression profile and on other studies designed for investigate the correlation between implantation and inflammation, by highlighting that the success of implantation is secondary to the development of an injury-like inflammatory reaction. In the last part of his lecture, Prof. Ubaldi presented very interesting data on the endometrium-blastocyst dialogue and more in particular on the factors mediating this dialogue, by

The phases of blastocyst implantation require a bi-directional dialogue...



Aachache et al., 2006 © 2014 S. Ubaldi

highlighting that the phases of blastocyst implantation require a bi-directional dialogue mediated through cytokines and other messengers. Prof. Ubaldi presented a huge amount of data demonstrating that these new messengers mediating the blastocyst-endometrium dialogue aiming at implantation are the mRNAs. In conclusion, the speaker pointed out that these results are very impressive, but for a definitive validation it is necessary to perform a prospective multicenter study.



Volcano plot showing a comparison of the miRNAs in SBMs from implanted (n=1/4 25) and unimplanted blastocysts (n=1/4 28). Blue dots indicate assays detectable in SBMs from both groups. Two miRNAs were identified as statistically significantly more abundant in the SBM from implanted blastocysts: miR-20a and miR-30c. © 2014 S. Ubaldi

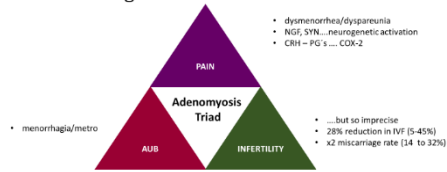
- What is the consequence of the rapid developmental evolution of omics technology platforms from the speaker point of view?
- Could implantation be boosted by an inflammatory-like response?
- What are the messengers involved in the bi-directional dialogue between blastocysts and endometrium?
- How many human gene translation and biological pathways are regulated by mRNA?

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Adenomyosis and subfertility: prevalence, diagnosis, treatment and fertility outcomes

4. Diagnosis



Prevalence, diagnosis, treatment and fertility outcomes for Adenomyosis and subfertility, was the topic discussed by Prof. Velasco. The speaker coming from Madrid (Spain) highlighted that it is very difficult to know the exact prevalence of Adenomyosis due to different information coming from literature, as well as guidelines. Going deeper in his talk Prof. Velasco spoke about

diagnosis, by focusing on the invasive and on the non-invasive procedures and on the so called Adenomyosis triad constituted by pain, infertility and AUB. Speaking about the non-invasive procedures, Prof. Velasco presented data on MRI and discussed about the 7 ultrasound features linked with the Adenomyosis diagnosis. In the second part of his lecture, the speaker talked about treatment, its

4. Diagnostic Criteria

Table 2 Epidemiological data from the study population

Variable	Adenomyosis n (%)	OR	P
Age < 40 y	154/699 (22.0)	0.67 (0.50-0.91)	p < 0.01
Age ≥ 40 y	94/316 (29.7)	1.50 (1.11-2.02)	p < 0.01
Smokers %	25/93 (26.8)	1.1 (0.70-1.84)	p = 0.56
Pregnancies			
0	233/963 (24.1)	0.7 (0.38-1.31)	p = 0.44
≥ 1	13/46 (28.2)	1.23 (0.63-2.38)	p = 0.53
Recurent miscarriage (RM)	26/68 (38.2)	2.03 (1.21-3.39)	p < 0.005
ART failure	107/305 (34.7)	2.14 (1.59-2.89)	p < 0.0001
Endometriosis	34/97 (35.1)	1.77 (1.14-2.77)	p = 0.01
Fibroids	48/266 (18)	0.60 (0.42-0.85)	p < 0.005

Puente et al. Reprod Biol Endocrinol 2016

Age

Poor ART

E2 disesase

6. Impact on fertility outcome

And clinically?

	Adenomyosis n=152	Endometriosis n=144	Controls n=147
Blastomeres D3	7.6	7.5	7.4
# embryos transferred	1.97	1.93	1.90
Implantation	26.9%	33.3%	30.8%
CPR	40%	44.2%	44.4%
Miscarriage rate	13.1%	6.1%	7.2%

Martinez-Conejero et al. 2011

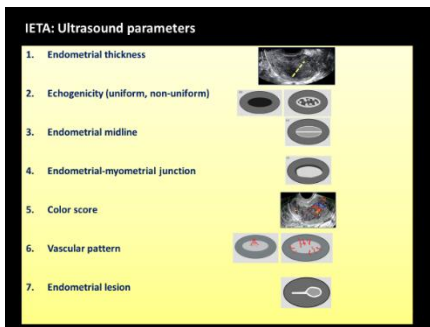
long-term safety and its main related issues. Finally, Prof. Velasco presented very interesting data on the impact of Adenomyosis on the fertility outcome. In conclusion, the speaker pointed out that nowadays there is an increased awareness of Adenomyosis and also the sonographic criteria for a precise diagnosis are clear, but there is the need for research-medical treatments.

- What do guidelines say on Adenomyosis?
- What's about the MRI accuracy in the Adenomyosis diagnosis?
- What are the 7 ultrasound features of the Adenomyosis diagnosis?
- What are the main issues linked to the Adenomyosis treatment?
- What is the impact of Adenomyosis treatment on fertility from a clinical point of view?

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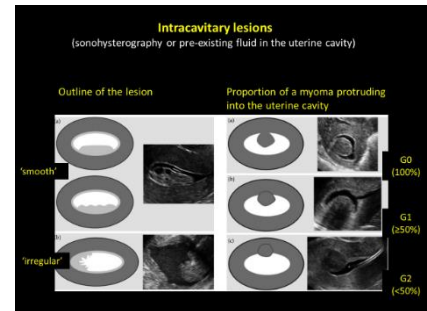
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Terms, definitions and measurements to define endometrial and intrauterine lesions: suggestions from the International Endometrial Tumor analysis (IETA Group)

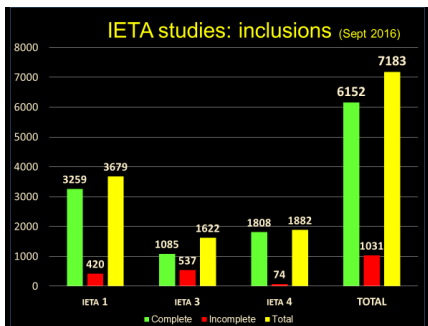


Prof. Moro from Rome (IT), spoke about the terms, definitions and measurements of the endometrial and intrauterine lesions, by presenting very interesting data given by the International Endometrial Tumor analysis (IETA) group. At the beginning of her lecture, the speaker presented the IETA terminology linked to any endometrial tumor, by focusing on the ultrasound parameters. Going deeper in her presentation the speaker

talked about many indexes like endometrial thickness, echogenicity divided into uniform and non-uniform, endometrial midline, endometrial-myometrial junction, colour score, vascular pattern and finally about endometrial lesions. Prof. Moro talked also about the applications of the



IETA terminology, by presenting very interesting data given by Imaging studies performed in patients affected by endometrial and intrauterine cancer or intracavitary lesions like polyps and myomas. In conclusion, Prof. Moro, pointed out that the IETA terminology is a standardized method for describing the endometrium, the endometrial tumors and for predicting stage, myometrial invasion and grading of the endometrial cancer.



- What are the main IETA terminology related to any endometrial pathology?
- What are the ultrasound parameters of the IETA terminology?
- What's about the application of the IETA terminology presented by the speaker?
- What's about the correlation between IETA terminology and the intracavitary lesions?
- What's about the IETA studies discussed by the speaker?

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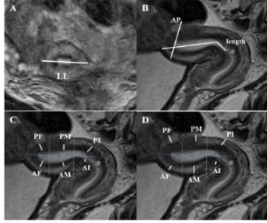
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AUB, junctional zone and Transvaginal sonography

T2 weighted turbo spin echo MR without fat suppression, + buscopan injection

- corpus size latero-lateral (LL)
- the length and the anteroposterior (AP) uterus
- junctional zone (J) and outer myometrium (D) thickness.



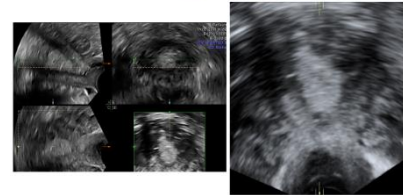
Uterine walls were divided into three parts: equally in length (blue line), and the measurement was performed at a central point in each part.
 JZ: junctional zone at the fundus, PM: posterior wall at the midcorpus, PE: posterior wall at the isthmus, AI: anterior wall at the fundus, AM: anterior wall at the midcorpus, AI: anterior wall at the isthmus.

AUB, junctional zone (JZ) and Transvaginal sonography was the topic discussed by Prof. Exacoustos in his lecture. The speaker coming from Rome (IT), talked about the main characteristics of JZ and its Imaging, the association between JZ and AUB with a particular focus on fibroids, endometrial malignancy and adenomyosis and finally about the association between JZ and endometriosis. Speaking about JZ and AUB, Prof. Exacoustos presented a huge amount of imaging data on all these features, by

ENDOMETRIAL CANCER

highlighting the tight correlation between the histologic specimens and ultrasound imaging. The speaker presented also the results of a multicenter study designed for the assessment of the uterine JZ detectable alterations in patients with endometriomas or deep endometriosis with

Evaluation of myometrial invasion



the 2D and 3D TVS evaluation and highlighted the tight correlation between TVS and these pathologies. In conclusion, Prof. Exacoustos pointed out that in the future the 3D TVS evaluation will be applied in the study of the effects of pregnancy on the structure and function of the JZ together with other very interesting topics like the correlation between fibroids and infertility.



To assess by 2D and 3D TVS detectable alterations of the uterine JZ in patients with:

- only endometriomas (OMAs) and
- with only deep endometriosis (DIE)

- 38 patients (OMA GROUP)
only endometrioma at TVS and LPS
- 42 patients (DIE GROUP)
only deep infiltrating endometriosis
no endometriomas at TVS and LPS
- 20 patients (CONTROL GROUP)
no pelvic endometriosis at TVS and LPS

multicenter study
 n° 100 nulliparous patients
 age 20-35 years



- What are the main characteristics of the uterine junctional zone presented by the speaker?
- What's about the association between JZ and AUB?
- What's about the association between JZ and endometriosis?
- What is the impact of the intramural fibroids on the junctional zone?
- What's about the correlation between JZ and adenomyosis?
- What are the main results of the multicenter study on 100 nulliparous patients aged 20 to 35 years old, presented by the speaker?

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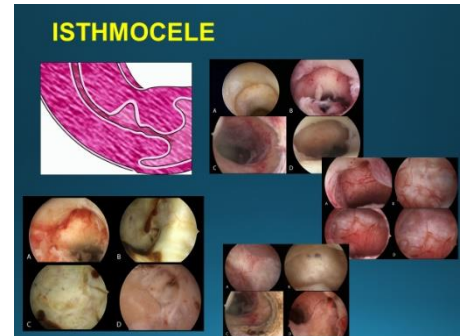
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AUB and Hysteroscopy

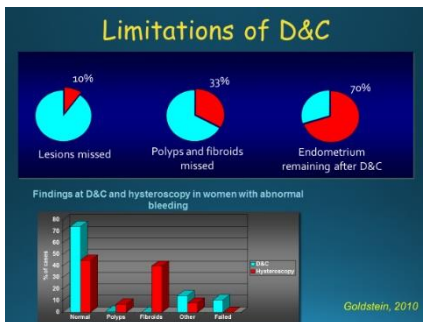


Prof. Di Spiezio Sardo from Naples (IT), presented very interesting data on AUB and hysteroscopy, by highlighting the confusion in the terminology of the AUB definition. Going deeper in his lecture Prof. Di Spiezio Sardo presented very interesting imaging data on the applicability of hysteroscopy in patients affected by abnormal uterine bleeding and highlighted the superiority of this technique compared to

ultrasonography. In the main part of his talk, the speaker presented data on the direct viewing of endometrium lesions like polyps, hyperplasia or myomas thanks to the hysteroscopy application. Prof. Di Spiezio Sardo presented also very interesting



imaging data on adenomyosis, isthmocele and other uncommon lesions. Finally, the speaker talked about the target-eye biopsy, the office operative hysteroscopy, the limits of the procedure of dilation and curettage and about the application of hysteroscopy in women with menorrhagia for the detection of submucous myomas.

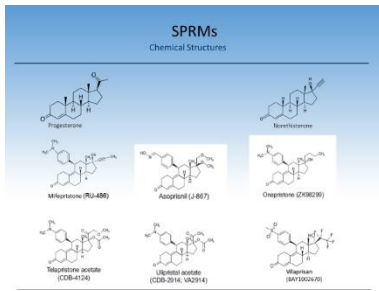


- What are the main lesions detectable with hysteroscopy?
- What are the main limits of the dilation and curettage procedure from the speaker point of view?
- What are the main characteristics of the office operative hysteroscopy?
- What's about the target-eye biopsy?
- What are the main definitions of the Abnormal Uterine Bleeding?

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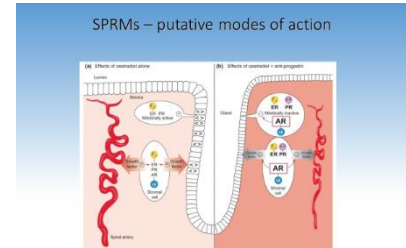
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Endometrial morphology after treatment with selective progesterone receptor modulators



The main topic at the core of Prof. Williams presentation, was the endometrial morphology after treatment with selective progesterone receptor modulators. The speaker, coming from Edinburgh (UK), presented very interesting data on SPRMs, a family of compounds binding PR with specific agonist and antagonist activities and a wide range of potential clinical applications, the first one on the

endometrium. Going deeper in his lecture, Prof. Williams spoke about the SPRMs' mechanisms of action, starting from the activities developed by the binding of Progesterone with its receptor. In the main part of his lecture, the speaker talked about the effect of SPRMs on endometrium, by highlighting that it is not fully characterized and that it presents some variations according to any specific agent. Prof. Williams spoke also about the



antiproliferative effects of SPRMs on endometrium and the possible mechanism of action. Finally, the speaker presented very interesting data given by clinical studies running in patients treated with any single SPRM agent, like Mifepistone, Asoprisnil and Ulipristal acetate. In conclusion, Prof. Williams pointed out that the SPRMs effects may vary somewhat according to any agent and that the antiproliferative effect appears consistent.

Reversibility of UPA-induced PAEC

% Patients having non-physiological endometrial appearances	PEARL I					Gudite
	Placebo	UPA 5 mg	UPA 10 mg	URS 5 mg	UPA 10 mg	
Screening	8.4%	10.0%	8.5%	6.1%	6.4%	6.4%
Week 12 (end of treatment)	14.6%	14.2%	70.4%	65.1%	64.7%	17.7%
Week 18	7.2%	14.2%	12.8%	17.3%	9.9%	11.2%

Non-physiological (ie. PAEC)	PEARL II Extension			
	UPA 10 mg + Placebo	UPA 10 mg + NETA	UPA 10 mg + Placebo	UPA 10 mg + NETA
Screening	One cycle after 14 UPA course	One cycle after 14 UPA course	One cycle after 14 UPA course	One cycle after 14 UPA course
4 (7.1%)	20 (30.8%)	11 (23.4%)	7 (14.3%)	15 (28.3%)
				11 (27.5%)

- What are the further potential uses for SPRMs in contraception and in the treatment of endometriosis from the speaker point of view?
- What's about the antiproliferative effect of these drugs based on the data presented by the speaker?
- What's about the PRM-associated endometrial changes presented by the speaker?
- What are the main characteristics of Ulipristal acetate?
- What are the main mechanisms of action of SPRMs?

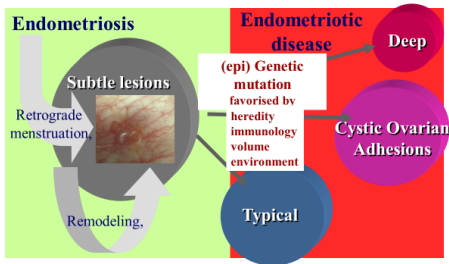
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Endometrial cell migration and endometriosis

The Endometriotic Disease Theory

Koninckx P.R., Kennedy S., Barlow D., Gyn Obstet Invest 1999;47:1-10

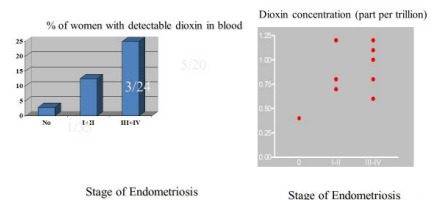


The main topics at the core of Prof. Koninckx presentation, were the endometrial cell migration and endometriosis. The speaker, coming from Kuleuven (Belgium), presented very interesting data, starting from the different presentations of endometriosis, its prevalence and histology with the aim to suggest the need for the revision of the endometriosis definition. Going deeper in his lecture Prof. Koninckx spoke about the pathophysiology of

all the types of endometriosis, starting from the theories on the modulators like peritoneal fluid, immunology and genetics, with the aim to highlight the need for a new endometriotic disease theory. In the main part of his lecture, Prof. Koninckx spoke about epigenetics involving endometrium cells, stem cells, bone marrow and pale cells and raised this question to the audience: why does a cell change behaviour? The speaker presented very interesting data on the correlation between pollution and endometriosis and, more in particular, on the dioxin concentrations in women

Dioxin Concentrations in women with endometriosis

Mayani A, Barel S, Saback S, Almagor M, Human Repr 1997, 12, 373-375



affected by endometriosis and on the relationship between dioxin and radiation as mutagenic factors. Prof. Koninckx spoke also about endometrium in endometriosis patients and more in particular on all the genetic factors released by this type of endometrium, like ICAM-1, P450aromatase transcripts, IL-6, IL-11 transcripts and heat shock protein 27 and presented very interesting data on the genes involved in endometriosis. Finally, Prof. Koninckx spoke about the risk of cancer driven by surgery.

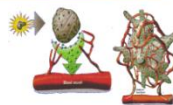
Angiogenic factors

- Bioassay
- VEGF
- TGF

Chicken allantoic membrane
Oosterlynck, Waer, Koninckx 1994



Like most benign tumors



Koninckx P.R., Kennedy S., Barlow D., Gyn Obstet Invest 1999;47:1-10

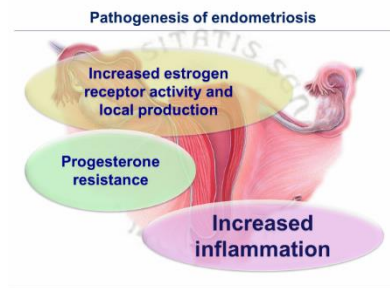
- What is the link between endometriosis, cancer stem cells and progression?
- What are the main angiogenic factors?
- What's about the Endometriotic Disease Theory?
- What is the correlation between endometriosis and epigenetics?
- What is the correlation between pollution and endometriosis?
- What are the main characteristics of the endometrium in endometriotic patients?

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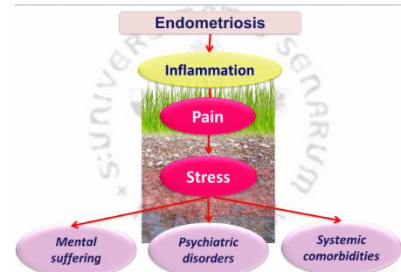
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Endometrium, inflammation and endometriosis



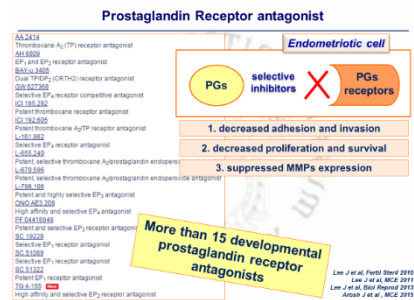
on the correlation between endometriosis and immunological disorders like lupus, rheumatoid arthritis and multiple sclerosis with a particular attention to the deep mechanisms linking all these diseases. Prof. Petraglia spoke also about chemotaxis, apoptosis and their clinical effects on endometriosis, about cytokines and their correlation with endometriosis, about pain, neurogenesis and their

Endometriosis, mental health and comorbidities



Prof. Petraglia, coming from Siena (IT), spoke about Endometrium, inflammation and endometriosis, by presenting a huge amount of data on the pathogenesis of endometriosis and the actors involved in this process. Going deeper in his lecture, Prof. Petraglia spoke about immunology and its linkage with the pathophysiology of endometriosis. In the main part of his talk, the speaker presented very interesting data

peripheral and central mechanisms in patients affected by endometriosis. Finally, the speaker presented very interested data on endometriosis and the stress related comorbidities. In conclusion, Prof. Petraglia pointed out that endometriosis is a benign disease but with a systemic diffusion that involve patients with a lot of direct and indirect very important symptoms, deeply affecting their quality of life.



- What's about immunology and its involvement in the pathogenesis of endometriosis based on the data presented by the speaker?
- What are the main immunological disorders linked with endometriosis?
- What's about the correlation between apoptosis and endometriosis?
- What are the main prostaglandins linked with the onset of endometriosis?
- What's about the prostaglandin receptor antagonists presented by the speaker?
- What is the correlation between cytokines and endometriosis?
- What is the correlation between pain, its neurogenesis and endometriosis?

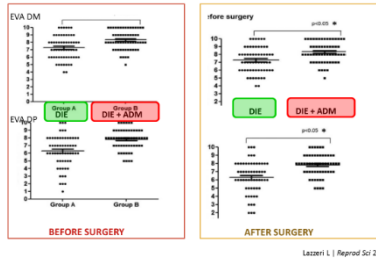
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The endometrium and the junctional zone myometrium in endometriosis and adenomyosis

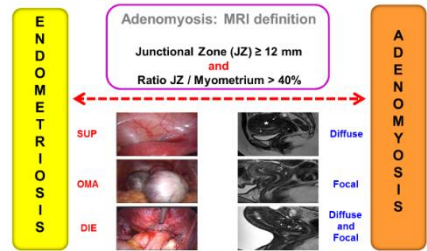
Adenomyosis is a cause of persistent pain after DIE surgery



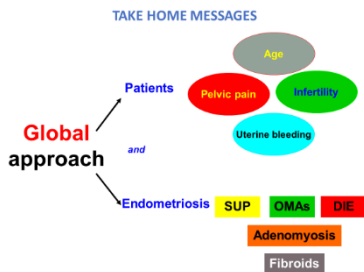
The endometrium and the junctional zone myometrium in endometriosis and adenomyosis, was the topic at the core of Prof. Borghese presentation. The speaker coming from Paris (France), at the beginning of his presentation talked about the structure of endometrium, myometrium and the uterine junctional zone. Going deeper in his lecture, the speaker talked about adenomyosis, its histological definition, its symptomatology

characterized by pelvic pain, uterine bleeding and infertility. Prof. Borghese spoke also about the MRI and the TVUS criteria for the diagnosis of adenomyosis. In the main part of his presentation, Prof. Borghese spoke about the heterogenous nature of adenomyosis and its tight relationship with endometriosis from the symptomatology and the phenotypic point of view. In the second part of his talk, the speaker presented very

What is the relationship between endometriosis phenotypes and adenomyosis?



interesting data on the close relationship between focal adenomyosis and bladder endometriosis, with a very different outcome between the anterior focal and the posterior focal adenomyosis. More in particular Prof. Borghese pointed out the importance of the global approach to endometriosis, by taking also care of the comorbidities like adenomyosis and fibroids. Finally, the speaker presented very interesting data on the different pathogenesis of diffuse and focal adenomyosis.



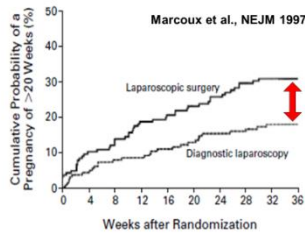
- What are the MRI criteria for the diagnosis of adenomyosis?
- What's about adenomyosis and the TVUS criteria?
- What are the main characteristics of the relationship between endometriosis and adenomyosis?
- What is the correlation between focal adenomyosis and endometriosis?

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Endometrial dysfunction and pregnancy failure in women with endometriosis

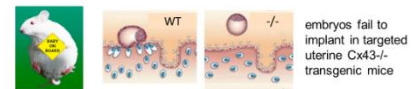
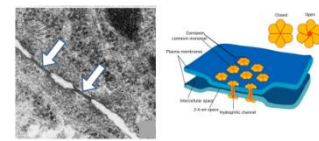
How Does Endometriosis Cause an Infertility Gap?



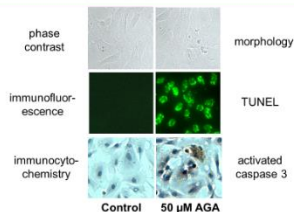
presented very interesting data on the sonographic and hysteroscopic assessment of the endometrial thickness and morphology. The speaker talked also about “ERA” that is the personalized embryo transfer project leading to the identification of the implantation defects sustained by cDNA microarrays and by the dysregulated implantation biomarker genes. Finally, the speaker talked about the correlation between the Gap junction and the endometrial function, by highlighting that Cx43 gap

The Endometrial dysfunction and the pregnancy failure in women with endometriosis, was the topic at the core of Prof. Taylor presentation. The speaker coming from New York (USA), presented very interesting data on endometriosis and infertility. More in particular the speaker talked about the three anatomic compartments involved like Ovaries, Uterus and Pelvic cavity, by highlighting that even in optimized setting of IVF, the implantation rates are reduced. Speaking about implantation, Prof. Taylor

Cx43 Gap Junctions are Critical for Uterine Receptivity and Fertility



Inhibition of Gap Junctions with AGA Causes Endometrial Stromal Cells to Undergo Apoptosis



junctions are critical for the uterine receptivity and fertility and presented very impressive data on the loss of Cx43 gap junctions in women affected by endometriosis and on the effects of the pharmacological GAP junction inhibition driven by AGA the 18α-glycyrrhetic acid blocker. In conclusion Prof. Borghese pointed out that the endometrial stromal cell differentiation in vivo and in vitro is associated with the Cx43 upregulation and this is mostly reduced in presence of endometriosis.

- What are the detrimental effects of endometriosis on the eutopic endometrial function?
- What is the effect of AGA on the GAP junctions?
- What is the significance of Cx43 based on the data presented by the speaker?
- What are the main dysregulated implantation biomarkers presented by the speaker?
- Why are the endometrial biopsies important from the histological and molecular information point of view?

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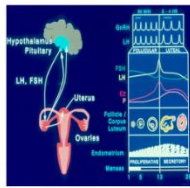
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The impact of perimenopausal ovarian function upon the endometrium: pathophysiology and treatment options

Understanding the Perimenopause

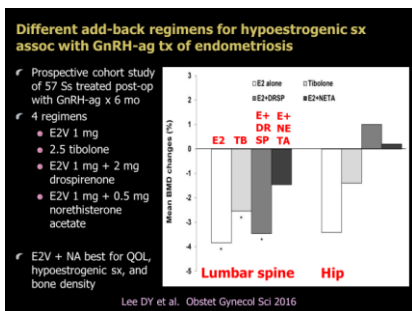
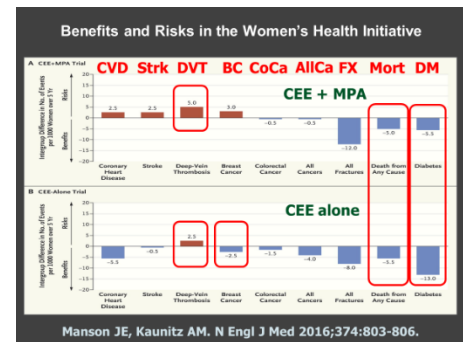
- Progressive interplay between ovaries and hypothalamic-pituitary unit
- Timing and tempo of perimenopause largely gated by oocyte quality and count, but for ovarian aging to be clinically evident, hypothalamic-pituitary unit must function
- Both increased FSH levels and altered hypothalamic feedback sensitivity drive aberrant folliculogenesis and hormonal aberrations



- Loops cycle - luteal out-of-phase follicular event
- Hale GE et al. Menopause 2009
- Lag cycle - long follicular phase with aberrant folliculogenesis, high estradiol (E2), and low or absent progesterone

The impact of perimenopausal ovarian function upon the endometrium: pathophysiology and treatment options was the topic Prof. Berga talked about. The speaker coming from New York (USA), presented very interesting data on two main topics: the evaluation of existing literature for recommendations on the hormonal interventions in peri-postmenopausal women with endometriosis and adenomyosis and the evaluation of the ovarian hormone secretion variability

based on age and health risks in women treated with oophorectomy and hormone therapy. At the beginning of her lecture, Prof. Berga presented the main critical concepts about the care of these patients and spoke about some concerns related to the postmenopausal hormone use and the malignant transformation of residual lesions. Going deeper in her lecture, Prof. Berga presented very interesting data on the hormonal profiles in the peri-postmenopausal period, by highlighting that when cycles become irregular, hormonal profile become unpredictable. In the main part of her talk the speaker presented very interesting



data on the treatment's options for peri-postmenopausal women affected by endometriosis, speaking about the benefits and risks of the menopause hormone therapy. More in particular Prof. Berga pointed out that there are no products specific for the peri-postmenopausal period and talked about the main characteristic that an ideal product should have. In conclusion, Prof. Berga pointed out that HRT should be considered after any type of ovarian suppression or

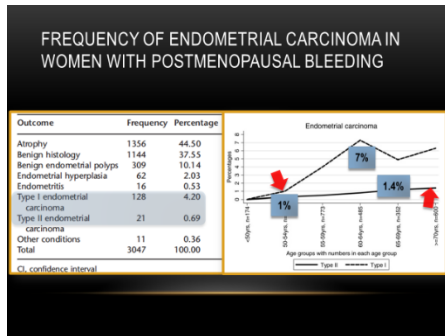
menopause in a woman with endometriosis.

- What are the main critical concepts and concerns in the care of women with endometriosis in the peri-postmenopausal time?
- What are the main concerns related to the presence of endometriosis in peri-postmenopausal women?
- What is the effect of the transition stage on the cognitive profile in postmenopausal women?
- What are the benefits of the hormonal therapies that suppress the ovarian function in peri-postmenopausal women?

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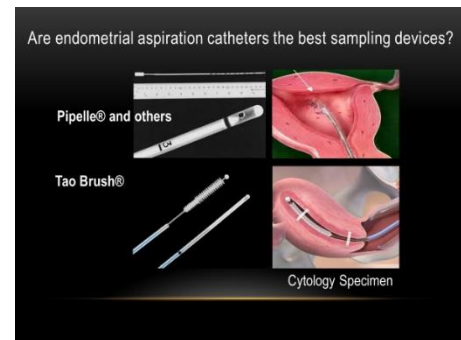
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Investigation of women with postmenopausal uterine bleeding: clinical practice recommendations

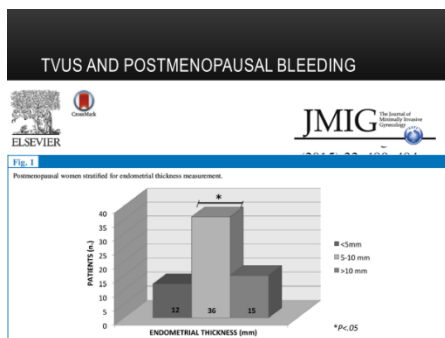


The Investigation of women with postmenopausal uterine bleeding and the related clinical practice recommendations, was the topic at the core of Prof. Munro presentation. The speaker coming from Los Angeles (USA), at the beginning of his lecture talked about the definition of postmenopausal bleeding and the frequency of endometrial carcinoma in these patients, by highlighting that this risk increases from 1% to 7% in 60 to 64 years old women. In the

main part of his presentation, Prof. Munro spoke about the clinical practice recommendations on women affected by postmenopausal uterine bleeding developed by the Kaiser Permanente, Southern California Evidence Based Practice Guideline. The speaker presented the main points of these recommendations, focusing on the intended use, the methodology, the hierarchy of evidence, the background and the context. More in particular Prof. Munro discussed the specific



recommendations on three types of postmenopausal bleeding: spontaneous, secondary to HRT and finally, related to the use of the selective estrogen receptor modulators. In the last part of his lecture the speaker talked about some issues like the long-term outcomes for women with EEC above 4 and normal EB, the diagnostic techniques and some specific circumstances like the type II endometrial carcinoma, the asymptomatic EEC thickness and the evaluation following endometrial ablation.



- What's about the use of TVUS in women with postmenopausal bleeding?
- What are the main issues related to the ultrasound-determined EEC thickness in women with endometrial carcinoma?
- What about the role of routine hysteroscopy in women with endometrial carcinoma?
- Are endometrial aspiration catheters the best endometrial sampling devices?
- What's about the accuracy of the endometrial biopsy?
- What's about patients using SERM such as tamoxifen?
- What's about the Transvaginal ultrasound for EEC?
- What EEC thickness should be considered abnormal?

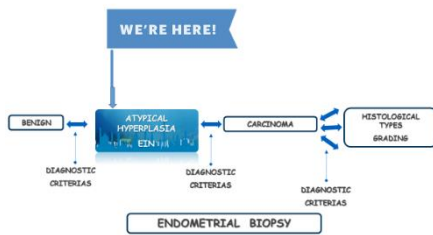
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Factors predictive of endometrial carcinoma in patients with atypical endometrial hyperplasia on preoperative histology

PRECURSOR LESION of the Endometrioid TYPE I Endometrial Adenocarcinoma.



Prof. Santini talked about the Factors predictive of endometrial carcinoma in patients with atypical endometrial hyperplasia on preoperative histology. The speaker coming from Bologna (IT), presented very interesting data on the WHO 2014 recommended terminology, the diagnostic reproducibility, the natural history of this disease and finally on the diagnostic decisions and the current practice. Going deeper in her lecture, Prof.

Santini spoke about the precursor lesions of the endometrioid type I endometrial carcinoma, by highlighting that the revised 2014 WHO classifications divided hyperplasia in two types: hyperplasia without atypia and atypical hyperplasia (AH) and considered the diagnostic term of endometrial intraepithelial neoplasia (EIN) as a synonymous of AH. Speaking about the diagnostic reproducibility, the speaker pointed out that the new WHO classification systems are highly predictive of the risk of progression to adenocarcinoma. From the natural history point of view, Prof. Santini highlighted that from the 30% to the 40% of patients diagnosed with AH/EIN may have coexisting adenocarcinoma, and the remaining

Problems in Defining the Natural History of Hyperplasia

PATHOLOGIC CRITERIA

The changes in path criteria means that...

Some of the lesions diagnosed as simple or complex hyperplasia without atypia correspond to AH/EIN

Diagnoses Reviewed for AH/EIN Criterion

- ▶ Atypical Hyperplasia = 78% AH/EIN
- ▶ Complex Hyperplasia = 44% AH/EIN
- ▶ Simple Hyperplasia = 4% AH/EIN

Diagnosis of AH-EIN: Endometrial Sampling and Imaging

Despite the limits of diagnostic hysteroscopy all data suggest its use in cases of AH TO BETTER

a. DESCRIBE the lesion

... it is possible for the pathologist to compare the histologic and morphological complexity with hysteroscopic description

CARTELLA INTEROSCOPICA DIAGNOSTICA



60% to 70% have a very high risk of cancer development. Finally, the speaker talked about the diagnostic decision and the current practice, by highlighting that there are some clinical features that may influence the course of the disease once the AH/EIN is diagnosed. In conclusion, Prof. Santini pointed out that AH/EIN must be considered as a premalignant lesion with the presence of coexisting invasive endometrial carcinoma in the 40% of cases.

- What are the main types of endometrial cancer presented by the speaker?
- What are the precursor lesions of the endometrioid type 1 endometrial cancer?
- What is the diagnostic reproducibility of the WHO 2104 recommendations?
- What are the main problems in defining the natural history of hyperplasia?
- What are the reviewed diagnoses related to the AH/EIN criteria?
- What is the risk of AH/EIN progression to carcinoma?
- What are the main clinical factors that may influence the course of the disease once AH/EIN is diagnosed?

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Evidence-based medicine and prognostic factors in endometrial cancer

Lack of ER	→	most aggressive tumor phenotype	Engel, Ann Oncol 2008
	→	Increased risk for recurrence	Walker, Ann Oncol 2014
	→	Decreased survival	Nguyen, Int J Gynecol Cancer 2009
Lack of PR	→	Increased risk for recurrence	Yam, Gynecol Oncol 2008
	→	Decreased survival	Kalish, Gynecol Oncol 2008
High Ki-67	→	Increased risk for recurrence	Shawhan, J Clin Oncol 2008
	→	Decreased survival	Indraganthy, J Clin Oncol 2008

Torricelli, Es J October 2013

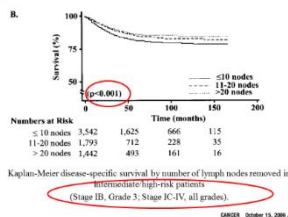
Dr. Di Donato talked about Evidence-based Medicine and the prognostic factors in endometrial cancer. The speaker coming from Rome (IT), presented very interesting data on the endometrial cancer epidemiology, by highlighting that this disease represents the most common gynaecological malignance. Going deeper in his lecture, Dr. Di Donato spoke about the prognostic

factors like estrogen receptors, progesterone receptors and Ki-67 factor and also about other biological prognostic factors mainly used in clinical research. In the main part of his lecture, Dr. Di Donato, presented very interesting data on the peritoneal cytology as a risk factor for recurrence for non-endometrioid endometrial cancer, by highlighting that lymphadenectomy is only recommended in high risk endometrial cancer patients. The speaker talked also about the role played by age as a key prognostic factor in EC patients, by

highlighting that patients over 65 years old present a worse outcome compared to the ones below 65. Speaking about obesity, hypertension and diabetes Dr. Di Donato pointed out that only diabetes and hypertension but not obesity have a worse impact on survival in EC patients. In conclusion, the speaker pointed out that from a prognostic point of view it is very important to take care of the tumor and at the same time of the patients' characteristics.

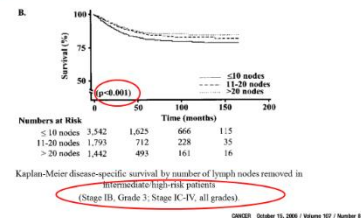
Therapeutic Role of Lymph Node Resection in Endometrioid Corpus Cancer

A Study of 12,333 Patients



Therapeutic Role of Lymph Node Resection in Endometrioid Corpus Cancer

A Study of 12,333 Patients



- What's about the effect of BMI on survival?
- What is the influence of age on the survival outcomes in EC patients?
- Do all patients require lymphadenectomy?
- What is the therapeutic role of lymph node resection in endometrioid corpus cancer?
- What is the role of the biological prognostic factors in endometrial cancer?
- What is the relationship between estrogen receptor, progesterone receptors, Ki 67 factor and EC prognosis?

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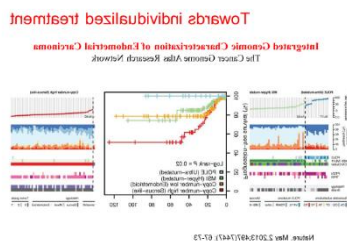
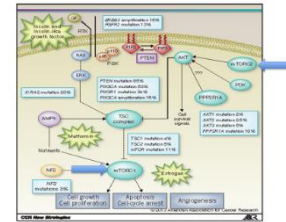
Cancer genes and biomarker for endometrial carcinoma

Cancer genes and biomarker for endometrial carcinoma was the topic Prof. Colombo talked about. The speaker coming from Milan (IT), presented very interesting data on the most common gynaecological cancers in developed countries, by highlighting that the majority of ECs is diagnosed in early stages, but the recurrences have an incidence between 15% to 20%. Going deeper

Pathologic Classification:	Molecular Classification:
Type 1 estrogen-dependent endometrioid EC eg. low-grade endometrioid alteration in PI3K/AKT/mTOR pathway	POLE (Ultramutated) high mutation load, TP53 mutations, extensive copy-number alterations Microsatellite Instability (MSI) Copy-number low & microsatellite stable Copy-number high serous like
Type 2 estrogen-independent non-endometrioid EC eg. serous, clear-cell, carcinosarcoma, mucinous, squamous...	

in her lecture, Prof. Colombo presented very interesting data on the type 1 and type 2 carcinomas biomarkers referred to the main gene mutations in endometrioid endometrial and in serous endometrial cancer. In the main part of her talk Prof. Colombo presented very interesting data on the potential therapeutic impact of the TCGA classification and more in particular on the potential drugs targeting the PI3K/PTEN/AKT/mTOR pathway by highlighting that only in few cases there is a sufficient response in term of efficacy and safety. The speaker presented other very interesting data given by studies aimed to evaluate the effect of the combination therapy of

Targeting the PI3K/mTOR Pathway



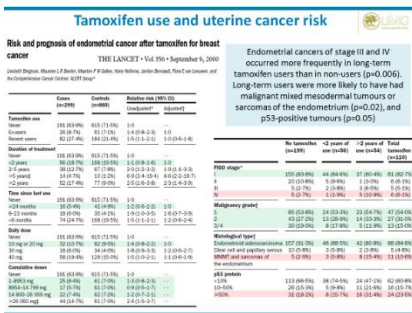
mTOR with metformin. In the second part of her lecture Prof. Colombo spoke about mTORE+ chemotherapy studies and FGFR1-3, VEGFR1-3 inhibitors studies and finally on PARP inhibitors. In the last part of her talk Prof. Colombo spoke also about immunotherapy, by presenting very interesting data on the response rates of the anti-PD1 drugs.

- What's about the effects of the mTOR + hormonal therapy based on the data presented by the speaker?
- What's about the integrated genomic characterization of endometrial cancer from the speaker point of view?
- What is the potential therapeutic impact of the TCGA classification?
- What are the main mTOR inhibitors presented by the speaker?
- What's about M-TOR in combination therapy based on the data presented by the speaker?
- What the results of the association between M-TOR and the hormonal therapy?
- What's about the Metformin study presented by the speaker?

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Molecular mechanisms of tamoxifen-associated endometrial cancer



The molecular mechanisms of tamoxifen-associated endometrial cancer were the topic of Prof. Zullo presentation. The speaker coming from Naples (IT), presented very interesting data on tamoxifen use and uterine cancer risk, by highlighting that the risk ratio in postmenopausal women with breast cancer taking tamoxifen is 4.0 times higher than that of an age matched population and it is dose and time dependent. Going deeper in his lecture, Prof. Zullo pointed out that in order to develop strategies for the minimization of the tamoxifen' effects on the endometrium it is mandatory to understand the molecular mechanisms of tamoxifen-induced endometrial cancer and presented very interesting data on these molecular mechanisms. Finally, the

How to screen tamoxifen users?

REVIEW ARTICLE

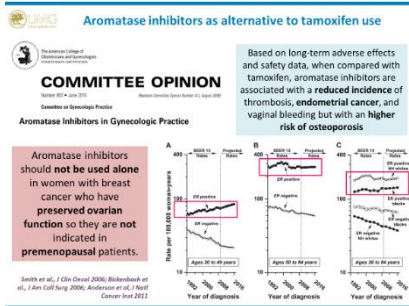
Investigation of Women with Postmenopausal Uterine Bleeding: Clinical Practice Recommendations

Michael S. Maurer, MD, FCCO, FASCO, The Southern California Postmenopausal Group, Alameda, California, Breast Imaging Group, Nov 1, 2014; doi:10.1016/j.jco.2014.08.001

No.	Recommendation	Method	Strength of evidence†
17	Women experiencing uterine bleeding while receiving tamoxifen (usually used as an adjuvant therapy for breast cancer) should be assessed primarily with endometrial sampling because, in such patients, TVUS is neither sensitive nor specific for endometrial cancer.	E	A
18	Women with persistent bleeding during tamoxifen therapy, and who have already undergone endometrial sampling, should be assessed with one or a combination of contrast echography (such as SES) and hysterectomy with appropriate sampling or excision of biopsy if found.	C	NA
19	Women with recurrent bleeding during tamoxifen therapy, and who have been demonstrated to have normal histologic findings and a structurally normal endometrium only, should have EB repeated annually.	E	B

Formerly there is controversy regarding the most appropriate approach to monitoring the endometrium in women using tamoxifen, with some investigators suggesting that routine endometrial sampling be performed on an annual basis. However, current evidence suggests that such an approach consumes resources without improving survival rates. Consequently, and at least for the present, only women receiving tamoxifen who experience uterine bleeding should be investigated.

speaker talked about the investigations to be performed for an effective screening of tamoxifen users at risk of endometrial cancer and presented very interesting data on the aromatase inhibitors as an alternative to tamoxifen use. In conclusion Prof. Zullo pointed out that in postmenopausal patients with breast cancer aromatase inhibitors can be preferred to tamoxifen but it is necessary to pay attention to bone density and overall costs.



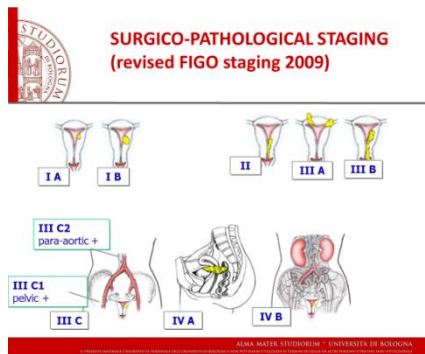
- How to screen tamoxifen users?
- What is the burden of the endometrial risk cancer in breast cancer patients independent by tamoxifen intake?
- What is the correlation between tamoxifen use and breast cancer recurrence and survival?
- What's about the correlation between tamoxifen and the uterine cancer patients risk, based on the data presented by the speaker?

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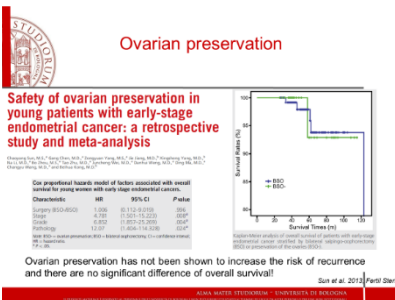
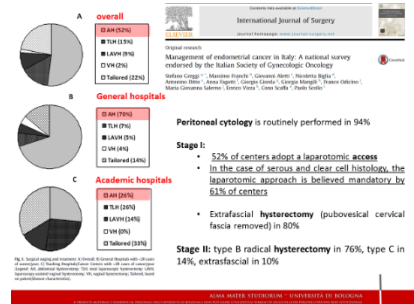
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Minimally Invasive Surgery in Endometrial Cancer



potential limitations and finally on two approaches: the MIS and the not-MIS one. Starting from the surgical-pathological staging approach, the speaker pointed out that MIS has to be recommended based on the surgical outcomes. Speaking about the adequacy of staging for MIS Prof. Mabrouk presented very interesting data on the use of laparoscopy in Italy and in his center, by highlighting that the data are very similar: laparoscopy is applied in more than 55% of cases. The speaker presented also data on the potential limitations of MIS, like obesity, more in particular with a BMI over 40, old age and other limitations related to anatomic or technique issues. Finally, the speaker talked



Prof. Mabrouk, coming from Modena (IT) spoke about minimally Invasive Surgery in Endometrial Cancer. The speaker at the beginning of his talk, addressed the audience with this question: there is there a role of the minimally invasive surgery in the management of the endometrial cancer? Prof. Mabrouk went deeper in his talk and presented very interesting data on the state of the art about the role of MIS, on the actual situation about its use, on the MIS potential limitations and finally on two approaches: the MIS and the not-MIS one. Starting from the surgical-pathological staging approach, the speaker pointed out that MIS has to be recommended based on the surgical outcomes. Speaking about the adequacy of staging for MIS Prof. Mabrouk presented very interesting data on the use of laparoscopy in Italy and in his center, by highlighting that the data are very similar: laparoscopy is applied in more than 55% of cases. The speaker presented also data on the potential limitations of MIS, like obesity, more in particular with a BMI over 40, old age and other limitations related to anatomic or technique issues. Finally, the speaker talked about lymphadenectomy, SLN mapping, ovarian and fertility sparing, by highlighting that in women under 40 years old without any predictable risk factor, the ovarian preservation could be the best option. In conclusion, Prof. Mabrouk pointed out that the true question is not the one raised at the beginning of his presentation, but this one: is there still a place for traditional surgery in the management of endometrial cancer?

- What is the role of the minimally invasive surgery in the management of the endometrial cancer?
- What's about the comparison between LPS and LPT in uterine cancer surgery?
- What are the potential limitations of the MIS staging presented by the speaker?
- Is obesity a limiting factor?
- What's about the relationship between elderly and LPS limiting factors?
- What are the main technique-related limitations of the LPS staging?
- What's about lymphadenectomy and LPS from the speaker point of view?

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The roles and limitations of robotic surgery for obese endometrial cancer patients: a common challenge in gynecologic oncology

ROBOTIC SURGERY FOR OBSE ENDOMETRIAL CANCER PATIENTS

World Health Organization

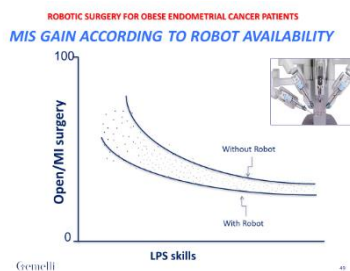
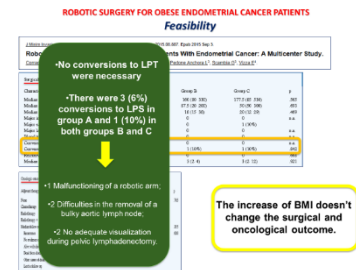
Classification BMI (2006) Global database on body mass index. World Health Organization, Geneva

Table 1: The International Classification of adult underweight, overweight and obesity according to BMI

Classification	Principal cut-off points	Additional cut-off points
Underweight	<18.50	<16.00
Severe thinness	<16.00	<16.00
Moderate thinness	16.00 - 16.99	16.00 - 16.99
Mild thinness	17.00 - 18.49	17.00 - 18.49
Normal range	18.50 - 24.99	18.50 - 24.99
Overweight	25.00 - 29.99	25.00 - 29.99
Pre-obese	25.00 - 29.99	27.50 - 29.99
Obesity	30.00 - 34.99	30.00 - 34.99
Obese class I	35.00 - 39.99	35.00 - 39.99
Obese class II	40.00 - 49.99	40.00 - 49.99
Obese class III	50.00 - 59.99	50.00 - 59.99

The roles and limitations of robotic surgery for obese endometrial cancer patients: a common challenge in gynaecologic oncology was the topic Prof. Scambia talked about. The speaker coming from Rome (IT), presented very interesting data on the correlation between endometrial cancer and obesity, by highlighting that more than 40% of endometrial cancer are present in obese patients. It is not only a problem

of obesity, Prof. Scambia, pointed out, the main problem is linked with the intra-abdominal adipose tissue distribution. Going deeper in his lecture, Prof. Scambia presented very interesting data on the role of MIS and more in particular on robotic surgery in endometrial cancer patients, by highlighting that the increase of BMI does not significantly change the post-operative complication rate when the robotic surgery is performed nor the surgical and the oncological outcome. In the second part of his presentation, the speaker talked about the limits of the robotic surgery pointing to the assessment of clinical and economical outcomes, but also and highlighted that the adoption of this new technology is able to reduce the costs, by spreading and sharing the professional knowledge and skills among physicians. Finally, Prof. Scambia talked about the future applications of robotic technology, by highlighting that at the Catholic University of Rome about 250 laparoscopic procedures have been performed for gynaecologic procedures most of them in obese patients. In conclusion, Prof. Scambia pointed out that, thanks to the robotic surgery, it is possible to further improve the ratio between MI/open surgery in obese endometrial cancer patients.



- What's about the perspective of robotic surgery presented by the speaker?
- Are there limits for robotic surgery from the speaker point of view?
- What's about lymphadenectomy in obese cancer patients treated with robotic surgery procedures?
- What is the role of MIS in endometrial cancer?
- What's about the correlation between intraabdominal adipose tissue and the risks of surgery?

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