AEPCOS NEWSLETTER

ANDROGEN EXCESS & PCOS SOCIETY

MAY-JUNE 2015 NEWSLETTER

INFLAMMATION AND ENDOMETRIAL DYSFUNCTION IN PCOS

This issue newsletter is dedicated to some new information about inflammation in PCOS..
Frank Gonzalez, M.D., Associate Professor of Obstetrics and Gynecology at the Indiana University and member of the Editorial Board, has interviewed Terhi Piltonen, M.D.., about the findings of her study on ithe role of inflammation in endometrial dysfunction of PCOS women..

The results of AEPCOS nominations for new President Elect and new Board member are shown.

A picture of AEPCOS Update Meeting that was held in Gdansk, Poland, June 12-13, 2015 is reported..

Finally, some practical information regarding 13th Annual Meeting of AEPCOS that will be held in Siracusa, Sicily, Italy, October 4-6, 2015 are presented..

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In this issue:

* Inflammation and endometrial dysfunction in PCOS
* Results of AEPCOS nominations

FORTHCOMING AEPCOS MEETINGS

- **Update Meeting of AEPCOS Society, Mumbai, India, August 15-16, 2015**
- **13th Annual Meeting of AEPCOS Society, Siracusa, Italy, October 4-6, 2015**
- **14th Annual Meeting of AEPCOS Society, Australia, November 2016**

AEPCOS NOMINATIONS

Almost 50% od AEPCOS voted for AEPCOS President Elect and for Board member.

Elisabet Stener Victorin is President Elect of AEPCOS Society, effective from October 1st, 2016

Marla Lujan is AEPCOS Board member, effective from October 6th, 2015

13th ANNUAL MEETING OF AEPCOS SOCIETY

Next annual meeting of AEPCOS Society will be held October 4-6, 2015 in Siracusa, Sicily, ITALY.

The conference venue is the Hotel des Etrangers, Passeggio Adorno 10-12, 96100 Siracusa, Italy. It is located in Ortigia, a small island that is the historical center of Siracusa.

The preliminary program, registration and hotel reservation form are available at: www.ae-society.org/annual-meeting. Abstract deadline is September 5, 2015. Abstract form is available in our website or may be requested to: info@ae-society.org

The most convenient airport is Catania airport that is linked by many daily flights to most European cities. Hourly flights from Rome and Milan permit easy connections for flights arriving from USA, South America and Asia. A taxi from the Catania airport to the historical center of Siracusa takes 40 minutes and costs 50-60 euro. There is hourly bus service to Siracusa which costs 6.2 euro while all main rental car companies have their office at Catania airport.

For further information, please check our website or contact: enrico.carmina@ae-society.org

PICTURES OF SICILY

AEPCOS UPDATE MEETING

Gdansk, Poland, June 12-13, 2015

A very successful update AEPCOS meeting was held in Gdansk, Poland, June 12 and 13, 2015. A summary of the meeting will be published in next issue of the Newsletter.

Participants to the AEPCOS UPDATE MEETING OF GDANSK. From left: Evy Diamanti-Kandarakis (Athens, Greece), Renato Pasquali (Bologna, Italy), Anuja Dokras (Philadelphia, USA), Dominik Rachon (Gdansk, Poland), Rosa Alba Longo and Enrico Carmina (Palermo, Italy), Lisa Moran (Adelaide, Australia), Helena Teede (Clayton, Australia) and Hector Escobar-Morreale (Madrid, Spain)

OTHER FUTURE MEETINGS

- EUROPEAN SOCIETY PEDIATRIC ENDOCRINOLOGY, BARCELONA, SPAIN, OCTOBER 1-3, 2015
- ASRM, BALTIMORE, MD, USA, OCTOBER 17-21, 2015
- ENDOCRINE SOCIETY, BOSTON, USA, APRIL 1-4, 2016
- EUROPEAN SOCIETY OF ENDOCRINOLOGY, MUNICH, GERMANY, MAY 28-31, 2016

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ROLE OF INFLAMMATION ON ENDOMETRIAL DYSFUNCTION IN PCOS

In this issue, Frank González interviewed Dr. Terhi Piltonen, who commented on her recent publication reporting that the endometrium of women with PCOS is a proinflammatory environment resistant to the anti-inflammatory effects of progesterone that can culminate in poor endometrial decidualization. These findings implicate inflammation in the development of implantation-related infertility and endometrial cancer in PCOS.

Piltonen T , Chen JC, Khatun M, Kangasniemi M, Liakka A, Spitzer T, Tran N, Huddleston H, Irwin JC, Giudice LC. Endometrial stroma fibroblasts from women with Polycystic Ovary Syndrome have impaired progesterone mediated decidualization, aberrant cytokine profiles and promote enhanced immune cell migration inn vitro. Human Reproduction 2015, 30:1203-1215

What was the objective of your study?

In addition to the anovulatory nature of PCOS-related infertility, the endometrium in women with PCOS has been shown to present with several abnormalities that may contribute to subfertility and risk for endometrial cancer in these women. In PCOS, endometrium has been shown to display altered steroid receptor expression and progesterone resistance (Apparao et al., *Biol Reprod* 2002:66:297; Savaris et al., *J Clin Endocrinol Metab* 2011:96:1737; Villavicencio et al., *Gynecol Oncol* 2006:103:307), and we have recently shown increased inflammation in proliferative phase endometrial samples (Piltonen et al., *J Clin Endocrinol Metab* 2013:98:3765).

As progesterone is crucial for decidualization and the implantation process, and as unopposed estrogen action due to lack of progesterone is thought to be crucial for the pathogenesis of endometrial cancer, the present study aimed to investigate if isolated endometrial stromal fibroblasts in women with PCOS exhibit altered estrogen (E2) and/or progesterone (P4) responses during 14-day in vitro decidualization. Furthermore, matrix metalloproteinase (MMP) expression was also assessed as these proteinases are usually suppressed by progesterone, and they have been shown to be involved in tissue remodeling and cancer pathogenesis. Given our previous findings showing increased cytokine expression in proliferative phase PCOS endometrium, we also aimed to assess if altered inflammatory responses were involved concomitantly with altered progesterone action.

Can you summarize your findings?

Three different study groups were formed according to E2-P4-induced decidualization response in endometrial stromal fibroblasts: 1) decidualized control samples; 2) decidualized PCOS samples; and 3) non-decidualized PCOS samples

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The experiments revealed that indeed, a subset of endometrial samples from women with PCOS have a blunted decidualization response to E2-P4 exposure shown by a lack of morphological changes and low insulin-like growth factor binding protein-1 (IGFBP-1) levels. In PCOS non-decidualized samples, P4 inhibited MMP secretion resulting in higher MMP-2 and -3 levels despite a normal estrogen-mediated increase in P4 receptor expression.
As for the inflammatory profile, even though decidualized PCOS samples had normal steroid hormone response showing high IGFBP-1 expression, they still presented with decreased IL-6 and granulocyte-macrophage colony-stimulating factor (GM-SCF) secretion compared with controls. The non-decidualized PCOS cultures, on the other hand, showed increased IL-6 and -8, MCP-1, RANTES and GM-CSF secretion at baseline and/or in response to E2 or E2-P4 compared with decidualized control and/or PCOS samples. In addition to individual cytokine/chemokine testing, the conditioned media from non-decidualized PCOS samples was also tested for its chemoattractic properties using CD4+ lymphocytes and CD14+ monocytes. The testing showed increased chemoattractic properties of the media from non-decidualized PCOS cultures when compared with controls. To explore if cytokines were able to inhibit decidualization *per se*, we also treated control cells with IL-6 and/or -8 for 14 days. This experiment revealed that the exogenous cytokines were not able to inhibit decidualization of endometrial stromal fibroblasts indicating that high levels of these cytokines in non-decidualized PCOS samples were not a likely cause for the aberrant steroid hormone response.

What is the novelty of these findings?

This is the first *in vitro* study showing altered inflammatory profile in isolated PCOS endometrial stromal fibroblasts in a presence of normal decidualization. Furthermore, we were able to show that some women with PCOS may present with altered P4 response with blunted decidualization in their endometrium with a concomitant increase in MMP expression and inflammation that may explain some of the adverse reproductive outcomes and increased risk for endometrial cancer in these women.

How do these findings relate to what has already been published in the scientific literature, and what are the implications of your findings as it relates to PCOS?

Unfortunately, there are only few studies in the literature investigating PCOS endometrium and no studies are found in regards to *in vitro* decidualization in PCOS. However, the microarray study by Savaris et al, suggested progesterone resistance in PCOS endometrium and our study supported this by showing blunted response to progesterone, although not complete resistance. Furthermore, inflammatory cascades have also been shown to be involved in cancer formation including that of the endometrium. Therefore, the lack of anti-inflammatory action of progesterone on PCOS endometrium and concomitant increase in cytokine and chemokine secretion may be key findings in understanding the mechanisms for subfertility and increased risk of preeclampsia and endometrial cancer in women with PCOS. We caution that this was a small preliminary study meriting a larger sample size with clinical endpoints to further evaluate the clinical relevance of our findings.