

CONFERENCIAS

REPRODUCTIVE OUTCOME IN POLYCYSTIC OVARY SYNDROME

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Chronic anovulation and infertility are the main issues in young PCOS women. There is evidence that anovulation in PCOS is not the consequence of increased androgen ovarian secretion but of the derangement of early follicle development that is characteristic of this disorder. It has been hypothesized that an inappropriate response in small follicles to LH could result in terminal differentiation of the granulosa cells and thence in premature arrest of follicle growth and anovulation. However, it is unlikely that the derangement of early follicle development is the only cause of chronic anovulation in PCOS. Many data suggest that increased insulin circulating levels play a major role in the anovulation of women with PCOS, too.

We have suggested that in the majority of women with PCOS the mechanism of anovulation may be the consequence of an interplay between genetic mechanisms affecting the early follicle development and environmental factors inducing obesity or altered fat distribution and chronic hyperinsulinemia.

Because of it, in some women with PCOS, lifestyle measures or insulin sensitizing drugs may be effective in inducing ovulation and fertility. However, in most young patients classic treatments with clomiphene or gonadotropins are needed and in some patients IVF has to be used.

Many anovulatory patients with PCOS become ovulatory in their late reproductive age and some patients will present a complete remission of all clinical and endocrine symptoms. The appearance of ovulatory cycles in women who were anovulatory and had menstrual irregularities from their puberty is a surprising phenomenon that probably depends on changes of ovarian function that progressively happen during adult age. At the end, the reproductive outcome of PCOS patients will be better than expected with the large majority of patients getting children and normal reproductive life.

SHORT TERM AND LONG TERM COMPLICATIONS OF POLYCYSTIC OVARY SYNDROME

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PCOS presents a lifetime risk of type II diabetes, cardiovascular diseases, chronic liver disease and endometrial cancer. However, in term of events, there is proven evidence only for type II diabetes (but mainly for occurrence in earlier age than in general population) and for endometrial cancer (2.7 fold).

At the contrary, the evidence regarding chronic liver diseases and cardiovascular events is much lower with few information for liver diseases and many contrasting reports for cardiovascular events.

Regarding cardiovascular (CV) diseases, it is still unclear whether CV events are increased in women with PCOS. Completely different data have been published and the quality of many studies is relatively low. Some recent evidence suggests a larger number of cardiovascular events (4 fold) in young population with PCOS. However, studies at this age present an inherent difficulty linked to the low number of CV events in young population. In addition, most data are based on hospitalized population and this approach may have some biases.

In aged PCOS patients the data are also contrasting but most recent studies show a slight increase of CV diseases. However, the number of events is much lower than that expected on the basis of risk calculation during young age. The mechanisms of the discrepancy between CV risk and late events in PCOS are unclear but a progressive normalization of CV risk during late reproductive age may have a main role.

MICROBIOMA PLACENTARIO: NUEVOS PARADIGMAS EN REGULACIÓN INMUNE DURANTE EL EMBARAZO

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The immunologic paradigm of pregnancy led to the conceptualization of pregnancy as an organ transplant which requires, for its success, a systemic immune suppression of the maternal immune system. Growing scientific evidence suggests that in many ways the placenta functions as a tumor rather than a transplant and the immune regulation of the maternal-fetal interface is the result of the coordinated interaction between all its cellular components, including bacteria. The role of microbiota in reproduction is in its infancy, but there is growing literature that supports its relevance. We discuss a potential normal function of bacteria in the establishment of immune-tolerance and the compelling evidence that a viral infection might be the underlying cause of perturbation of homeostasis. There is compelling evidence that many infectious diseases of humans are caused by more than one microorganism and are defined as polymicrobial infections. We propose that pregnancy complications, such as preterm birth, are the result of polymicrobial infections. We examine the potential cellular and molecular mechanisms by which a viral infection of the placenta might disrupt the normal interaction between the cellular component of the implantation site and bacteria. As we better understand the normal homeostasis between the maternal immune system, placenta and commensal, we will be able to elucidate the pathogenic conditions and design better approaches to treat pregnancy complications associated with infection.

OVULACIÓN Y ORIGEN EXTRAOVÁRICO DEL CÁNCER DE OVARIO

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The mortality rate of ovarian cancer remains high due to late diagnosis and recurrence. A fundamental step toward improving detection and treatment of this lethal disease is to understand its origin. A growing number of studies have revealed that ovarian cancer can develop from multiple extra-ovarian origins, including fallopian tube, gastrointestinal tract, cervix and endometriosis. However, the mechanism leading to their ovarian localization is not understood. We utilized in vitro, ex vivo, and in vivo models to recapitulate the process of extra-ovarian malignant cells migrating to the ovaries and forming tumors. We provided experimental evidence to support that ovulation, by disrupting the ovarian surface epithelium and releasing chemokines/cytokines, promotes the migration and adhesion of malignant cells to the ovary. We identified the granulosa cell-secreted SDF-1 as a main chemoattractant that recruits malignant cells towards the ovary. Our findings revealed a potential molecular mechanism of how the extra-ovarian cells can be attracted by the ovary, migrate to and form tumors in the ovary. Our data also supports the association between increased ovulation and the risk of ovarian cancer. Understanding this association will lead us to the development of more specific markers for early detection and better prevention strategies.

EMBARAZOS MÚLTIPLES EN AMÉRICA LATINA: DISTRIBUCIÓN Y MOTIVOS DE SU DISMINUCIÓN

Dra. María Teresa Urbina

Los embarazos múltiples son la principal complicación de la reproducción asistida ya que están asociados con una mayor morbilidad materna y neonatal.

La Red Latinoamericana de Reproducción Asistida (RED LARA) recopila y analiza, anualmente desde 1990, los datos de los centros de fertilidad de sus países miembros. En 1995, este Registro Latinoamericano de Reproducción Asistida (RLA) muestra que la tasa de multigestación estaba cerca del 30%, una consecuencia del alto número de embriones transferidos ($\bar{X}=3,3$).

Los datos de RLA permitieron a RED LARA y a las sociedades de fertilidad de sus países miembros desarrollar programas educativos que condujeran a la disminución de la tasa de multigestación, incluyendo tópicos sobre sistemas de selección de los embriones (según sus características morfológicas o de los pronúcleos), cultivo de blastocistos y vitrificación de ovocitos y de embriones.

Más adelante, esta iniciativa se acompañó con una campaña "Hacia la transferencia de un solo em-

brión". A su vez, el Programa de Acreditación de los centros de RED LARA fue exigiendo estándares de calidad más estrictos cada año, en cuanto a los criterios máximos permitidos en relación a las tasas de embarazos dobles y de alto orden.

Con todos estos esfuerzos, la tasa de multigestación de alto orden por fecundación in vitro ha disminuido. El último reporte del RLA (2013) incluye 57.456 ciclos iniciados, caso por caso, de 158 centros en 15 países. Las tasas de multigestación disminuyeron a 20,7% en embarazos dobles y 1,1% en los de alto orden. Pero, considerando sólo los casos de donación de óvulos, las tasas de multigestación son 30% en embarazos dobles y 1,4% en embarazos de alto orden.

Estos resultados son un paso adelante, pero aún faltan más esfuerzos. La mayoría de las parejas ve con agrado los embarazos dobles, sin embargo, las tasas de prematuridad son 7,5% en los embarazos simples y de 36,58% en los dobles. Mientras, la transferencia electiva de un solo embrión ocurre sólo en 2% de los casos.

Dadas las graves consecuencias de la multigestación es importante persuadir a los pacientes a aceptar la transferencia de un sólo embrión, educándolos sobre los riesgos asociados con los embarazos dobles, y sobre las tasas de éxito acumuladas que se pueden lograr con la transferencia de un sólo embrión, cada vez. Un beneficio adicional de esta estrategia sería facilitar la cobertura estatal y de los seguros de los costos de los tratamientos de fertilidad. De esta manera, estaremos contribuyendo al acceso universal a servicios de salud reproductiva, una de las Metas de Desarrollo Sostenible.

MENSTRUAL ALTERATIONS DUE TO ENERGY DEFICIT IN YOUNG WOMEN

Dra. Vincenza Bruni

The close tie in all living beings between energy availability and reproductive function explains the development in humans of a refined, complex mechanism that continually monitors individual metabolic homeostasis. This mechanism conditions both food behavior and functioning of the hypothalamic-pituitary-ovarian axis. Conditions of reduced availability of energy due to either increased energy expenditure or decreased food intake have swift repercussions on ovulation and the menstrual cycle. These homeostatic mechanisms also condition bone turnover.

The thin, efficient body image supported by current fashion has determined an increase in the prevalence of menstrual dysfunctions related to controlled food intake and/or excessive physical activity by individuals who believe that they are adhering to healthy behavior. The epidemiology of these disturbances shows that both precocious (perimenarcheal period) and above all late onset are on the increase. Young subjects are certainly more vulnerable to the psychological stimuli of mass media, and they are also biologically more vulnerable to the impact of stress (even metabolic) and to hypothalamic dysfunction.

Therefore, both reflection on cultural models and early individuation of subjects who are falling into the trap of food intake control are important. Diagnosis is not easy because often the subjects are of normal weight due to increase in lean mass and present an endocrine profile close to normal ranges. Study of body composition (by BIA and DXA) and of certain indicators that function as signals of energy deficit (leptin, sometimes also FT3 and IGF-1) can help.

MARKERS OF INSULIN RESISTANCE IN ADOLESCENTS AND YOUNG WOMEN WITH PCOS

Dra. Vincenza Bruni

The endocrine and metabolic changes that take place during puberty (increase in ovarian volume, increase in LH and androgen levels, physiological insulin resistance) and postmenarcheal anovulation can be confounding factors in the diagnosis of PCOS in this age group. Thus, the diagnosis of PCOS should be established only after accurate longitudinal evaluation, at least 2 years after menarche, and in the presence of three specific criteria, i) androgen excess (biochemical or evident progressive hirsutism), ii) two years of oligomenorrhea, iii) polycystic ovary.

The high prevalence of insulin resistance and hyperinsulinemia in adult and adolescent PCOS subjects, both obese and not, is well known although few, if any, guidelines include this condition as a criterion for PCOS diagnosis.

There is ample evidence of metabolic disturbances associated with insulin resistance, such as metabolic

syndrome, altered glucose tolerance, and type 2 diabetes. The problem of NAFLD (non-alcoholic fatty liver disease) in adolescence is less well known. Obesity and insulin resistance are the principal factors in NAFLD; androgen excess may be another contributing factor to this condition. Patients with PCOS, especially (but not only) those who are obese, should undergo androgen level testing. We investigated a population of 39 adolescents with PCOS (Rotterdam criteria), mean age 17.5 ($\pm$ 1.9) years and 17 controls, mean age 18.7 ($\pm$ 3.14) years, to evaluate the possible presence and degree of NAFLD.

The PCOS patients showed higher values of body mass index (BMI) (25.54 ± 4.89 vs 21.3 ± 2.50 , $p=0.002$), waist to hip ratio (WHR) (0.82 ± 0.07 vs 0.76 ± 0.04 , $p=0.017$) and BIA for fat mass ($24.54 \pm 7.49\%$ vs $16.58 \pm 5.47\%$), and lower BIA values for lean mass ($73.94 \pm 8.35\%$ vs $83.57 \pm 5.49\%$, $p<0.0001$) compared to controls. Lipid profile, glycaemic metabolism, and other biochemical parameters were evaluated by standard methods. Ultrasound-measured IMT and vascular compliance were assessed by pulse wave velocity (PWV) at common carotid and femoral arteries, as early morphological and functional markers of atherosclerotic vessel wall damage. Patients showed higher carotid and femoral IMT (0.85 ± 1.15 mm vs 0.47 ± 0.08 mm, $p=0.001$; 0.76 ± 0.16 mm vs 0.54 ± 0.09 mm, $p<0.0001$), worse carotid and femoral compliance (7.83 ± 2.78 m/s vs 4.71 ± 0.58 m/s, $p<0.0001$; 8.03 ± 2.31 m/s vs 5.75 ± 0.95 m/s, $p<0.0001$), and higher degrees of liver steatosis (3.25 ± 1.57 vs 0.49 ± 0.51 , $p<0.0001$) than controls. In conclusion, evaluation of these parameters is important for early prevention of CVS damage.