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From the Editor: On Women's Health, progress and challenges
Del Editor sobre la Salud de la Mujer, progresos y retos

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An important review on breast cancer treatment, artificial intelligence in human reproduction techniques, use of surgical mesh products for the transvaginal repair of pelvic organ prolapse, abrupt hormonal changes with bilateral salpingo-oophorectomy in women before age 50, association of high risk HPV infection with cardiovascular disease, meager results with treatments to prevent osteoporosis and other consequences of estrogen deprivation, are some of the Editor´s choice considered in this section on women's health.

GYNECOLOGY

DENND1A MAY PLAY A CENTRAL ROLE IN PCOS

Polycystic ovary syndrome (PCOS) is highly heritable, but the common genetic susceptibility variants identified to date can only explain a small proportion of this heritability. Common variants in *DENND1A* have previously been associated with PCOS diagnosis in genome-wide association studies. Subsequent studies indicated that *DENND1A* is an important regulator of human ovarian androgen biosynthesis. New evidence that *DENND1A* (P=5.31×10^{-5}, *Padj*=0.039) plays a central role in PCOS suggests that rare noncoding variants contribute to disease pathogenesis[1].

PRACTICE ADVISORY: FDA ORDERS MANUFACTURERS OF SURGICAL MESH FOR TRANSVAGINAL REPAIR OF PELVIC ORGAN PROLAPSE TO STOP SELLING ALL DEVICES

On April 16, 2019, the U.S. Food and Drug Administration (FDA) ordered the manufacturers of all remaining surgical mesh products indicated for the transvaginal repair of pelvic organ prolapse (POP) to stop selling and distributing their products in the U.S. immediately. ACOG Practice Advisory stated that it is important to note that the FDA announcement applies only to mesh placed vaginally to treat POP. The FDA order does not apply to transvaginal mesh for stress urinary incontinence, nor to mesh placed abdominally (sacrocolpopexy via laparotomy or endoscopy) for prolapse repair[2].

WOMEN'S REPRODUCTIVE LIFE, NEW BURDENS AND COMPLICATIONS

Abrupt hormonal changes associated with bilateral salpingo-oophorectomy (BSO) in women before age 50 may lead to structural abnormalities of the medial temporal lobe later in life. Amygdala volume was smaller in the BSO group (median [IQR], 1.74 cm3) than the control group (2.15 cm3; P < .001). The parahippocampal-entorhinal cortex was thinner in the BSO group (3.91 mm) than the control group (3.97 mm; P = .046). Entorhinal white matter fractional anisotropy was lower in the

BSO group (0.19) than the control group (0.22; P = .03). Longitudinal evaluation is needed to determine whether cognitive decline follows[3].

HPV AND CARDIOVASCULAR RISK

Human immunodeficiency virus (HIV) infection could decrease to zero transmissions by 2030 in the USA[4]. On the other hand, human papillomavirus (HPV) is the most common sexually transmitted infection worldwide, and certain oncogenic strains of HPV are causative agents of anogenital cancers in women. A study using HNANES (National Health and Nutrition Examination Survey) 2003 to 2006 reports an association between HPV, especially oncogenic strains, and an increased prevalence of self-reported diagnosis of myocardial infarction and stroke among community-dwelling women living in the USA[5]. We would also like to discuss a cohort study of 63 411 women age 30 or older without cardiovascular disease (CVD) at baseline who underwent a high-risk HPV test and were followed annually or biennially from 2011 to 2016. Among them, high-risk HPV infection (prevalence 7.6%) was significantly associated with an increased risk of developing CVD (HR 1.25; 95%CI 1.03-1.52), especially in obese individuals and those with metabolic syndrome (MetS), indicating that high-risk HPV might affect CVD risk with possible effect modification by obesity and MetS[6].

IVF, ARTIFICIAL INTELLIGENCE AND BLASTOCYSTS, CONCEIVED BIRTHS AND CANCER

We have recently published about grading embryos at the blastocyst stage using artificial intelligence (AI) in Peru, which would yield better results than subjective grading by embryologists[7]. A recent study[8] published in Nature evaluated the efficacy of using AI to accurately predict the quality of human blastocysts and select the best single embryo for transfer. An AI approach was trained to recognize embryo quality using time-lapse images of 10 148 embryos—6 000 from 877 good-quality embryos and 6 001 from 887 poor-quality embryos. The AI was based on deep neural networks (DNNs), various node layers through which data pass in a multi-step process of pattern recognition. Training of the DNN involved 50 000 steps. The results indicated that the algorithm was able to correctly identify good-quality and poor-quality images with 96.94% accuracy (1 871 correct predictions

out of 1 930 images). The fact that this technology is already in use in Peru is a great advantage for the local development of our specialty.

A study followed 2 776 (4%) children of Finnish administrative registers who were conceived by medically assisted reproduction between 1995 and 2000; 1 245 children were added as sibling comparison. Children conceived by medically assisted reproduction had worse perinatal outcomes than those conceived naturally, even after adjustments for observed child and parental characteristics—e.g., difference in birthweight of −60 g (95% CI −86 to −34) and 2·15 percentage point (95% CI 1·07 to 3·24) increased risk of preterm delivery. In the sibling comparison, the gap in birth outcomes was attenuated, so the relation between medically assisted reproduction and adverse birth outcomes was statistically and substantively weak for all results considered. These outcomes included a difference in birthweight of −31 g (95% CI −85 to 22) and a 1·56 percentage point (95% CI −1·26 to 4·38) increased risk of preterm delivery. Results indicate that this increased risk is largely attributable to factors other than the medically assisted reproduction treatment itself[9].

In another study that included 275 686 children from the USA conceived via IVF and a cohort of 2 266 847 children, in which 10 births were randomly selected for each IVF birth, the overall cancer rate was 251.9 for the IVF group and 192.7 for the non-IVF group (hazard ratio, 1.17; 95% CI, 1.00-1.36). The rate of hepatic tumors was higher among the IVF group than the non-IVF group (18.1 vs 5.7; hr, 2.46; 95% CI, 1.29-4.70). This study found a small association of IVF with overall cancers of early childhood. However, it did observe an increased rate of embryonal cancers, particularly hepatic tumors, which may be attributed to IVF as well as to underlying infertility[10].

MENOPAUSE AND PREVENTIVE MEASURES FOR AGING WOMEN – DO THEY WORK?

Menopause has been associated with osteoporosis and other systemic consequences of estrogen deprivation. Bone loss has been associated with fractures, disability and physical limitation, as well as a shorter life expectancy. Conjugated estrogens and estradiol seem to improve bone quality, but there is no evidence supporting the effect of calcium and vitamin D, medications to

prevent osteoporosis, on present health complications. A recent study with 3 700 participants aged 50 years and over observed that, although bone mineral density (BMD) is strongly associated with fracture and post-fracture mortality, the burden of fractures attributable to low BMD has not been investigated yet. Overall, 21% of women and 11% of men in a study had osteoporotic BMD. In univariate analysis, 21% and 16% of total fractures in women and men, respectively, were attributable to osteoporosis. Osteoporosis presenting in advanced age (>70 years) accounted for 34% and 35% of fractures in women and men, respectively. However, the conjunction of these two factors accounted for ca. 60% of hip fractures. About 99% and 66% of postfracture mortality in women and men, respectively, could be explained by advanced age, osteoporosis and fracture, where advanced age contributed to this risk the most. The researchers conclude that a substantial health care burden of fracture is present in individuals aged over 70 independently of whether they have osteoporosis or not. This suggests that treating individuals with osteoporosis is unlikely to reduce a large number of fractures in the general population[11].

We are continuously hearing about the importance of calcium intake in postmenopausal women to prevent osteoporosis. In a study of 1994 osteopenic women aged over 65, postmenopausal bone loss was unrelated to dietary calcium intake. This suggests that strategies to increase calcium intake are unlikely to impact on the prevalence and morbidity of postmenopausal osteoporosis[12].

The Aspirin to Reduce Risk of Initial Vascular Events (ARRIVE) trial, initiated a decade ago, sought to answer long-standing questions about whether aspirin is cardioprotective in a primary prevention setting. Aspirin at a daily dose of 100 mg was not seen to reduce the long-term risk for cardiovascular (CV) or cerebrovascular events in a trial that randomly assigned more than 12 000 nondiabetic adults with multiple CV risk factors but no history of CV events. The risk for stroke was not reduced either[13].

Experimental and epidemiological studies suggest female sex hormones have long-lasting neuroprotective and anti-ageing properties. Surgically-induced menopause leads to a premature cessation of exposure to female sex hormones and could thus impact late-life cognitive function. Yet, evidence remains controversial. A systematic review of the literature on the association of surgical menopause (defined as bilateral oophorectomy before the onset of menopause) with risk of dementia, cognitive performance, cognitive decline, and Alzheimer's disease neuropathological indices later in life found eleven eligible studies (N = 18 867). Early surgical menopause (≤45 years of age) was associated with a statistically significantly higher risk of dementia (HR: 1.70). Surgical menopause at any age was associated with faster decline in verbal memory, semantic memory, and processing speed, whereas early surgical menopause was further associated with faster global cognitive decline. A younger age at surgery was associated with faster decline in global cognition, semantic and episodic memory, worse performance in verbal fluency and executive function, and accumulation of Alzheimer's neuropathological traits[14]. Preventive measures of early alterations in cognitive function and risk of dementia include avoiding early surgical menopause.

Breast cancer treatment

The prestigious journal JAMA has recently published an important paper with the educational objective to review the clinical management of patients with breast cancer that we consider most important to inform[15]. Breast cancer is categorized into three major subtypes based on the presence of molecular markers for estrogen or progesterone receptors and human epidermal growth factor 2 (*ERBB2*; formerly *HER2*): hormone receptor positive/*ERBB2* negative (70% of patients), *ERBB2* positive (15%-20%), and triple-negative (tumors lacking all three standard molecular markers; 15%). More than 90% of breast cancers are not metastatic at the time of diagnosis. For people presenting without metastatic disease, therapeutic goals are tumor eradication and preventing recurrence. Triple-negative breast cancer is more likely to recur than the other two subtypes: it has an 85% 5-year breast cancer–specific survival rate for stage I, as opposed to a 94% to 99% rate for hormone receptor positive and *ERBB2* positive cancers. Systemic therapy for nonmetastatic breast cancer is determined by subtype: patients with hormone receptor–positive tumors receive endocrine therapy, and a minority receive chemotherapy as well; patients with *ERBB2*-positive tumors

receive *ERBB2*-targeted antibody or small-molecule inhibitor therapy combined with chemotherapy; patients with triple-negative tumors receive chemotherapy alone. Local therapy for all patients with nonmetastatic breast cancer consists of surgical resection, possibly coupled with postoperative radiation if lumpectomy is performed. Increasingly, some systemic therapy is delivered before surgery. Tailoring postoperative treatment based on preoperative treatment response is an active area of research. Metastatic breast cancer is treated according to subtype, aiming to prolong life and palliate symptoms. Median overall survival for metastatic triple-negative breast cancer is approximately one year, while the other two subtypes have approximately five years. In conclusion, optimal therapy for each patient depends on tumor subtype, anatomic cancer stage and patient preferences[15].

News in Obstetrics

We suggest our patients to wait 2 years after a livebirth and 6 months after a miscarriage as a practical recommendation for better reproductive outcomes in the next pregnancy. Of course, some of our patients return pregnant before achieving the intervals recommended; fortunately, the outcome of the new pregnancy is usually successful. For the interpregnancy interval following a stillbirth without complications, we have traditionally considered waiting 2 years. Previously published, consistent evidence supports that pregnancies conceived less than 18–24 months after a livebirth are at increased risk of adverse outcomes[16]. However, a new paper refutes this. In an international cohort study of 14 452 births in women who had a stillbirth in the previous pregnancy, median interpregnancy interval after stillbirth was 9 months (IQR 4–19), and 9 109 (63%) women conceived within 12 months of the stillbirth. Of the 14 452 births, 228 (2%) were stillbirths (SB), 2 532 (18%) were preterm births (PTB), and 1 284 (9%) were small-for-gestational-age (SGA) births. Compared with an interpregnancy interval of 24–59 months, intervals shorter than 12 months were not associated with increased odds of subsequent stillbirth (pooled adjusted OR 1·09 [95% CI 0·63–1·91] for <6 months; 0·90 [0·47–1·71] for 6–11 months), PTB (aOR 0·91 for <6 months; 0·91 for 6–11 months), or SGA (0·66 for <6 months; 0·64 for 6–11 months). There was no difference in the association between interpregnancy interval and birth outcomes by gestational length of the previous stillbirth[17].

The cause, treatment and prevention of preeclampsia continue to be studied. Angiogenic factors could have a high diagnostic accuracy, and test results for placental growth factor (PlGF) have recently shown to reduce substantially the time to clinical confirmation of preeclampsia. Where PlGF was implemented, a lower incidence of maternal adverse outcomes was observed, consistent with adoption of targeted, enhanced surveillance, as recommended in the clinical management algorithm for clinicians[18].

In a prospective cohort study conducted in 346 consecutive pregnant women evaluated for preeclampsia, the congo red dot (CRD) paper test (index test) was performed on fresh urine samples and results were compared to an expert adjudicated diagnosis for each case, and also compared to urine and serum analytes (placental growth factor and soluble fms-like tyrosine kinase-1). During the first triage visit, 32% (112/346) of women received a clinical diagnosis of preeclampsia. However, 63% (217/346) were admitted for in-patient diagnostic work-up or delivery. The CRD paper test was positive in 25% (86/346) of the cases. Adjudication confirmed preeclampsia in 28% (96/346) of all cases. The CRD paper test outperformed measured serum and urine markers (80·2% sensitivity, 89·2% specificity, 92·1% negative predictive value, 86·7% accuracy). The pre-test, positive and negative post-test probabilities were 27·7%, 74·0%, and 8·0%, respectively[19].

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