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From the Editor on Women's Health: pregnancy, complications, future Del Editor sobre la Salud de la Mujer, embarazo, complicaciones, futuro

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In the last few months, we have found interesting new studies on women's health related to pregnancy and its long and short-term complications. Our specialty needs to know these advances as input for our medical practice and to prevent consequences in the long term.

PREVENTING SEVERE MATERNAL MORBIDITY AND MATERNAL DEATHS

Considering the worrisome aspect of maternal near misses and deaths in our countries, medical research from other parts of the world may help prevent these negative outcomes. Severe maternal morbidity has increased in the United States over the past two decades by approximately 200%, to 144 cases per 10 000 delivery hospitalizations. Of the 19 844 580 live births in the United States between 2012 and 2016, 27 602 (0.15%) mothers were admitted to the ICU in the peripartum period. These patients were more likely to be of advanced age, smoke cigarettes, and have a sexually transmitted infection during pregnancy. They also had pregestational diabetes, gestational hypertension or preeclampsia, chronic hypertension and gestational diabetes, higher rates of obesity, excessive weight gain (more than 22.67 kg during pregnancy, weight at delivery greater than 136 kg), and BMI of 50.0 or higher. Finally, they were also more likely to have a prior cesarean birth, induction preceding delivery, a prior preterm birth, and longer interpregnancy intervals. The mean gestational age at delivery was 35.9 vs 38.5 weeks⁽¹⁾.

Between 2011 and 2014, there were 17.2 maternal deaths per 100 000 live births in the United States, and 3 in 5 of these were preventable, according to a CDC report. 31% of such maternal deaths occurred during pregnancy; 36%, during delivery or in the following week; 33%, between a week and a year after delivery. Cardiovascular events accounted for about one-third; 60% of hypertension-related deaths occurred within a week of delivery; over half of stroke-related deaths, 1 to 42 days after delivery; cardiomyopathy deaths occurred most frequently 43 days to 1 year after delivery. Severe bleeding, hypertensive disorders, and infection were the leading causes of death 1 to 6 days postpartum⁽²⁾. Also, of 1 059 713 women who delivered a live-born infant in California hospitals during 2010–2012, 330 died. The leading cause of death was obstetric-related problems (6.52 per 100 000 person-years), drug-related deaths were the second leading cause (3.68 per 100 000 person-years), and suicide was the seventh leading cause (1.42 per 100 000 person-years). Drugs and suicide were a major contributor to mortality in the postpartum period⁽³⁾.



NUTRITION, GESTATIONAL WEIGHT GAIN AND ADVERSE MATERNAL AND INFANT OUTCOMES, INCLUDING CANCER

Eating-for-two is a permanent issue for pregnant women and doctors. We know that the potential mother and the pregnant woman should have the best nutrition in quality and quantity. In the diets of pregnant or breastfeeding women and young children, many types of fish are both nutritious and low in mercury. The Dietary Guidelines for Americans recommends that women who are pregnant or breastfeeding eat 2 to 3 servings (8 to 12 ounces) of low-mercury fish per week⁽⁴⁾.

However, there are limits in nutrition. In a meta-analysis of data from 25 pooled cohort studies and 196 670 participants from Europe and North America, prepregnancy weight and the magnitude of gestational weight gain were associated with risk for any adverse outcome -preeclampsia, gestational hypertension, gestational diabetes, cesarean delivery, preterm birth, and small or large size for gestational age at birth⁽⁵⁾. Furthermore, searches in MEDLINE and other important databases identified a 264% increase in the odds of child obesity when mothers have obesity before conception⁽⁶⁾. In an analysis that included 1 827 875 infants, children born to mothers with a body mass index ≥ 40 had a 57% higher risk for leukemia. Newborn size $\geq 30\%$ higher than expected was associated with 2.2-fold and 1.8-fold hazard ratios for total childhood cancer and leukemia, respectively, compared to newborns with the expected size. Being $<30\%$ below the expected size also increased the overall cancer risk ($P < 0.0001$)⁽⁷⁾.

On the other hand, exercise during pregnancy can positively influence developing systems of the fetus, causing an improved neuromotor development. Because physical activity is a modifiable risk factor for childhood obesity, exercise during pregnancy may potentially reduce this risk⁽⁸⁾. Interestingly, expectant mothers who move house in the first trimester have a 37% higher chance of low birth weight and a 42% greater chance of premature birth compared with women who do not⁽⁹⁾.

LONG-TERM PHYSICAL HEALTH IN WOMEN WITH UNWANTED PREGNANCIES AFTER ABORTION

Antiabortion groups and individuals argue that abortion harms women⁽¹⁰⁾. In a prospective cohort study in 874 out of 1 132 women seeking abortion attended in 30 American abortion facilities (328 had first-trimester abortion, 383 had second-trimester abortion, and 163 gave birth), physical health was not worse in women who sought and underwent abortion, compared with women who were denied the procedure. Differences emerged suggesting worse health among those who gave birth⁽¹¹⁾. Among the women who presented for abortion just before or after the gestational age limit and were followed up for 5 years, those who had been denied an abortion were more likely to experience economic hardship and insecurity lasting years, as opposed to women who underwent the procedure⁽¹²⁾.

A 2018 report from the Centers for Disease Control and Prevention shows the American abortion rate declined 26% between 2006 and 2015, reaching a historic low. In the first half of 2019, several states passed some of the most restrictive abortion bans since 1973. CDC data shows that more women using contraception and more effective forms of contraception, like intrauterine devices, might help explain this trend. Obamacare and new restrictions on abortion may be another factor⁽¹³⁾. In 2018, Alabama voters passed an amendment to the state's constitution that "recognize[s] and support[s] the sanctity of unborn life and the rights of unborn children." Kansas, Missouri, and Louisiana have enacted similar language into their constitutions. These clauses variously classify fertilized eggs, zygotes, embryos, and fetuses as "persons" entitled to unspecified legal protections from the moment of conception⁽¹⁴⁾.

Regarding endometriosis and maternal complications, a cohort study of 196 722 pregnancies (Nurses' Health Study II) found an association between laparoscopically confirmed endometriosis and a greater risk of pregnancy loss (spontaneous abortion: RR 1.40, 95% CI 1.31–1.49; ectopic pregnancy: RR 1.46, 95% CI 1.19–1.80). Endometriosis was also associated with a greater risk of gestational diabetes mellitus (RR 1.35, 95% CI 1.11–1.63) and hypertensive disorders of pregnancy (RR 1.30, 95% CI 1.16–1.45)⁽¹⁵⁾.



BREAST CANCER CLINICAL PRACTICE GUIDELINES

Medscape has recently published a summary of the Breast Cancer Clinical Practice Guidelines (2019) released on May 1, 2019, by the National Comprehensive Cancer Network⁽¹⁶⁾. Guidelines show important new aspects of diagnosis and treatment. In Peru, breast cancer is the second most common type of cancer (men and women combined) and the most frequent among women (20%). According to the Peruvian League Against Cancer, there were 6 985 new cases and 4 daily victims of breast cancer in 2018⁽¹⁷⁾. This disease is the most commonly occurring cancer in women worldwide and the second most common cancer overall, with over 2 million new cases in 2018. The top three countries with the highest rates in 2018 (age-standardized rate >100 per 100 000) were Belgium, Luxembourg and the Netherlands⁽¹⁸⁾. In 2019, it is estimated that ca. 268 600 new cases of invasive breast cancer will be diagnosed in women in the U.S., along with 62 930 new cases of non-invasive (in situ) breast cancer. About 2 670 new cases of invasive breast cancer are expected to be diagnosed in men in 2019⁽¹⁹⁾.

BREAST CANCER CLINICAL PRACTICE GUIDELINES (2019)

- **Multigene testing**

For patients with hormone receptor (HR)-positive, node-negative, HER2-negative disease and tumors larger than 0.5 cm, clinicians should strongly consider the 21-gene assay.

- **Early-stage breast cancer in premenopausal women**

Greater emphasis is placed on adding ovarian function suppression to tamoxifen or exemestane in premenopausal women with early-stage breast cancer.

- **HR-positive breast cancer in postmenopausal women**

Postmenopausal HR-positive breast cancer is most commonly treated with up-front aromatase inhibitor therapy for 5 years. Extended endocrine therapy remains an area of uncer-

tainty and is not currently a strategy that can be recommended for most patients.

- **Axillary management of early-stage breast cancer**

Patients with operable disease who will undergo surgery as primary treatment should be stratified according to the presence or absence of clinically positive lymph nodes at diagnosis.

If the patient is clinically node-negative up front, sentinel lymph node biopsy is typically done first.

If the patient is undergoing preoperative therapy first, imaging of the axilla and up-front biopsy of any clinically or radiographically suspicious lymph nodes are recommended.

- **Advanced HR-Positive Breast Cancer**

For HR-positive disease, recommendations are evolving away from choosing among monotherapy options and toward the concept of partnering endocrine therapy with targeted therapies. Positive findings from pivotal trials led to the recommendation that cyclin-D kinase 4/6 (CDK4/6) inhibitors (palbociclib, ribociclib, and abemaciclib) be added to endocrine therapy as either first-line or second-line treatment; abemaciclib can also be used as monotherapy.

- **Triple-Negative Metastatic Breast Cancer**

For patients with advanced triple-negative breast cancer with BRCA1/2 mutations, poly (ADP-ribose) polymerase (PARP) inhibitors show clear benefit, as do the older platinum agents. Talazoparib is a preferred option, along with olaparib, for patients with HER2-negative disease and germline BRCA1/2 mutations. Optimal sequencing of PARP inhibitors is yet to be determined.

The programmed death ligand 1 (PD-L1) antibody atezolizumab has been found to be beneficial for those with triple-negative breast cancer expressing PD-L1.



BLOOD PRESSURE, HYPERTENSIVE DISORDERS, PREECLAMPSIA, CARDIAC DYSFUNCTION

BLOOD PRESSURE TRAJECTORY AND HYPERTENSIVE DISORDERS IN NULLIPAROUS WOMEN

Recently updated American College of Cardiology/ American Heart Association (ACC/AHA) guidelines redefine blood pressure categories as Stage 1 hypertension (systolic 130-139mmHg or diastolic 80-89mmHg), Elevated (systolic 120-129mmHg and diastolic <80mm) and Normal (<120/<80 mmHg), but their relevance to the obstetric population is uncertain⁽²⁰⁾. A prospective observational study of 8 899 nulliparous women with singleton pregnancies was conducted at eight clinical sites; the first study visit occurred at a mean gestational age (GA) of 11.6 ± 1.5 weeks and the second one, at a mean GA of 19.0 ± 1.6 weeks. A higher blood pressure category in the first trimester was significantly associated with a higher risk for all hypertensive disorders of pregnancy. Stage 1 hypertension was associated with the highest risk for preeclampsia with severe features, aRR 2.48 (95%CI 1.38-8.74). Women with normal blood pressure and an upward systolic trajectory had a 41% increased risk of any hypertensive disorder of pregnancy (aRR 1.41; 95%CI 1.20-1.65), compared to women with a downward systolic trajectory. Blood pressure categories with lower thresholds than those traditionally used to identify individuals as hypertensive may identify more women at risk for preeclampsia and gestational hypertension⁽²¹⁾.

PREECLAMPSIA, PRETERM BIRTH, CARDIOVASCULAR DISEASE AND LONG-TERM CARDIAC DYSFUNCTION

Cardiovascular disease is the leading cause of mortality worldwide; most of it is preventable by altering behavioral risk profiles and lifestyle modifications⁽²²⁾. Preventive efforts aimed at decreasing blood pressure and body mass index could reduce cardiovascular risk in women with history of hypertensive pregnancy disorders⁽²³⁾. In most pregnant women, the physiological stress their cardiovascular system undergoes is uncomplicated; however, in women who experience hypertensive disorders of pregnancy, preterm birth and other obstetric complications, this may serve to identify patients at risk for cardiovascular disease, coronary heart disease, stroke, and death caused by these conditions⁽²⁴⁾.

Women with preeclampsia and no major comorbidities before their first pregnancy are at a 5-fold increased risk of end-stage kidney disease (ESKD) compared with parous women with no preeclampsia⁽²⁵⁾.

Concluding this section, we cite a list of recommendations for the primary prevention of cardiovascular disease⁽²⁶⁾. Physicians should be interested in these recommendations and explain their importance to their patients.

TAKE-HOME MESSAGES FOR THE PRIMARY PREVENTION OF CARDIOVASCULAR DISEASE

1. The most important way to prevent atherosclerotic vascular disease (ASCVD), heart failure, and atrial fibrillation is to promote a healthy lifestyle throughout life.
2. A team-based care approach is an effective strategy for the prevention of cardiovascular disease. Clinicians should evaluate the social determinants of health that affect individuals to inform treatment decisions.
3. Adults who are 40 to 75 years old and are being evaluated for cardiovascular disease prevention should undergo 10-year atherosclerotic cardiovascular disease (ASCVD) risk estimation and have a clinician-patient risk discussion before starting on pharmacological therapy, such as antihypertensive therapy, a statin, or aspirin. In addition, assessing for other risk-enhancing factors can help guide decisions about preventive interventions in select individuals, as can coronary artery calcium scanning.
4. All adults should consume a healthy diet that emphasizes the intake of vegetables, fruits, nuts, whole grains, lean vegetable or animal protein, and fish, and minimizes the intake of trans fats, processed meats, refined carbohydrates, and sweetened beverages. For adults with overweight and obesity, counseling and caloric restriction are recommended for achieving and maintaining weight loss.
5. Adults should engage in at least 150 minutes of accumulated moderate-intensity physical activity per week or 75 minutes of vigorous-intensity physical activity per week.



6. For adults with type 2 diabetes mellitus, lifestyle changes such as improving dietary habits and achieving exercise recommendations are crucial. If medication is indicated, metformin is first-line therapy, followed by a sodium-glucose cotransporter 2 inhibitor or a glucagon-like peptide-1 receptor agonist.
7. All adults should be assessed at every health-care visit for tobacco use, and those who use tobacco should be assisted and strongly advised to quit.
8. Aspirin should be used infrequently in the routine primary prevention of ASCVD because of lack of net benefit⁽²⁷⁾.
9. Statin therapy is first-line treatment for primary prevention of ASCVD in patients who are 40 to 75 years old, with elevated low-density lipoprotein cholesterol levels (≥ 190 mg/dL), those with diabetes mellitus, and those determined to be at sufficient ASCVD risk after a clinician-patient risk discussion.
10. Nonpharmacological interventions are recommended for all adults with elevated blood pressure or hypertension. For those requiring pharmacological therapy, the target blood pressure should generally be $<130/80$ mm Hg.

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