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From the Editor on Women's Health: Potential detrimental health effects during pregnancy and menopause Del Editor sobre la Salud de la Mujer: posibles efectos perjudiciales sobre la salud en el embarazo y la menopausia

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Committed to informing our readers about women's health, we share the latest research in obstetrics and gynecology, in the hope that this knowledge accompanies us in our daily practice, in preventive medicine and evidence-based treatment.

DETRIMENTAL HEALTH EFFECTS DURING PREGNANCY

Life expectancy at birth in all countries is above the diagonal parity line – all over the world, a newborn girl can expect to live longer than a newborn boy⁽¹⁾. Because of this, preventive health care should be implemented since birth. In addition, during the reproductive period, gynecologists should advise future mothers to be in good health when getting pregnant and to avoid unintended or forced pregnancies and potential environmental threats to the fetus. A group of researchers has found that black carbon particles accumulate on the fetal side of the placenta; this suggests that ambient particulates could be transported towards the fetus⁽²⁾. Pregnant women who are exposed to higher air pollution levels during their second pregnancy may be at greater risk for preterm birth, when compared with their first pregnancy⁽³⁾.

In a representative study of 13 310 American women aged 18 to 44 years, 6.5% reported forced sexual initiation at about 15.6 years, which appeared to be associated with multiple adverse reproductive, gynecologic, and general health outcomes⁽⁴⁾. Estimations of either intimate partner violence or non-partner sexual violence against women vary between 24% in the Southern Latin America and the Caribbean (LAC) and 41% in the Andean LAC—higher than the global estimation of 35%⁽⁵⁾. In Peru, young women begin sexual intercourse at 18.5 years, and even earlier in rural and Amazonian areas⁽⁶⁾. Adolescent pregnancy was 12.6% in 2018⁽⁷⁾. It is important to know that prenatal and perinatal characteristics such as high birth order, teenage mothers, single mothers, low maternal and paternal education, low birthweight and small-for-gestational-age babies have been associated with increased suicide risk during the life course, supporting the developmental origin of health and disease hypothesis for suicide⁽⁸⁾.

According to new mortality estimates released by UNICEF, the World Health Organization (WHO), the United Nations Population Division, UNFPA and the World Bank Group, an estimated 2.8 million pregnant women and newborns die every year (1 every 11 seconds; 600 women every day), mostly of preventable causes⁽⁹⁾. Postpartum hemorrhage causes approximately 11% of maternal deaths in the United States and



is the leading cause of death on the day of birth. 54 to 93% of maternal deaths due to obstetric hemorrhage may be preventable. Given that approximately 40% of postpartum hemorrhage occurs in low-risk women, every laboring woman is at risk for obstetric hemorrhage. Quantifying blood loss, for example by using graduated drapes or weighing, provides a more accurate assessment of actual blood loss than visual estimation. However, current data do not support any one method for quantifying blood loss as superior to another⁽¹⁰⁾. A study performed in the Netherlands in women with persistent postpartum hemorrhage found that early fresh frozen plasma transfusion (within the first 60 minutes) was not associated with maternal deaths, hysterectomies, or arterial embolizations, compared with no or later plasma transfusion⁽¹¹⁾. In addition, nearly one quarter of all maternal deaths in the United States from 2013 to 2016 were related to sepsis, and over one third of those deaths occurred after hospital discharge⁽¹²⁾. Top steps that can be easily adopted by any hospital or health system are the following: focus on the major delivery complications, move from reaction to prevention, standardize protocols, empower the care team, encourage prenatal and postpartum care⁽¹³⁾. ACOG recommends checklists and protocols should be incorporated into systems as a way to help practitioners provide the best evidence-based care to their patients⁽¹⁴⁾. We present an ACOG-based protocol for massive postpartum hemorrhage in this current number of the Peruvian Journal of Gynecology and Obstetrics.

THINKING ABOUT THE FETUS

The estimated worldwide prevalence of low birth weight (LBW) in 2015 was 14.6%, compared with 17.5% (14.1–21.3) in 2000. In order to meet the global nutrition target of the World Health Assembly, we will need more than double the progress obtained between 2012 and 2025⁽¹⁵⁾. Consequently, healthy low-risk women with a low fetal abdominal circumference after 24 weeks' gestation need to be monitored carefully for fetal growth to identify small for gestational age infants with a risk for adverse perinatal outcomes⁽¹⁶⁾. In late preterm pre-eclampsia, planned delivery reduces maternal morbidity and severe hypertension compared with expectant management; in addition, while planned delivery had more neonatal unit admissions related to

prematurity, there were no indicators of greater neonatal morbidity⁽¹⁷⁾.

Out of 116 429 women between ages 25 and 42 in 1989 that reported detailed information on pregnancies and reproductive health at baseline and every 2 years thereafter in the Nurses' Health Study II, 196 722 pregnancies were reported in 2009. There were several adverse pregnancy outcomes related with laparoscopically confirmed endometriosis; these included spontaneous abortion, ectopic pregnancy, stillbirth, gestational diabetes mellitus, preeclampsia, gestational hypertension, preterm birth, and low birth weight⁽¹⁸⁾. Lower standardized birth weight for gestational age, fewer number of live births and infertility have also been associated with a high rate of endometriosis, namely 111 cases in 3 406 women born in Uppsala, Sweden, between 1933 and 1972⁽¹⁹⁾. Examining the relation of endometriosis with reproductive outcomes in Latin American women would further contribute to this discussion.

In scheduled cesarean sections at term, there was no significant difference in the change in maternal hemoglobin at postoperative day 1 when comparing delayed versus immediate umbilical cord clamping⁽²⁰⁾. On the other hand, a significantly higher rate of severe intraventricular hemorrhage (a sign of harm) was related to umbilical cord milking among preterm infants born at less than 32 weeks' gestation; this finding led to early termination of a study⁽²¹⁾.

Some worrisome circumstances during pregnancy deleterious to the fetus have been recently found. We use fluoride-containing dental creams for enamel protection and teeth whitening. Now, we have to be aware that fluoride exposure during pregnancy has been associated with lower IQ scores in children aged 3 to 4 years⁽²²⁾. In a retrospective cohort study using records from 469 789 mother-child pairs who delivered at the Kaiser Permanente Southern California (KPSC) Hospital (1991–2014), children exposed to hyperemesis gravidarum in utero had higher rates of autism spectrum disease than unexposed children (2.87 vs. 1.71/1 000 person-years; adjusted HR: 1.53; 95% CI: 1.37–1.70)⁽²³⁾. Data from 15 421 participants at the Boston and Providence sites of the Collaborative Perinatal Project showed an association between maternal bacterial infection during pregnancy and a significantly higher risk



for psychotic disorders in offspring depending on the severity of the infection and child's sex (males)⁽²⁴⁾. A study of maternal stress during pregnancy included 187 women with singleton pregnancies where 67% formed the healthy group (HG), 17% formed the psychologically stressed group (PSYG) because they evidenced perceived stress, depression and anxiety, and 16% formed the physically stressed group (PHSG), with relatively higher ambulatory blood pressure and increased caloric intake. There were less male births in the PSYG and PHSG groups; PHSG versus HG infants were born 1.5 weeks earlier ($P < 0.05$) and had decreased fetal heart rate-movement coupling ($P < 0.05$), and PSYG versus PHSG fetuses had more birth complications⁽²⁵⁾. We can mention two examples of maternal stress situations and adverse perinatal outcomes. The 2016 US presidential election appears to have been associated with an increase in preterm births among US Latina women. Anti-immigration policies were proposed and enforced in the aftermath of the 2016 presidential election⁽²⁶⁾. Despite having fewer at-risk baseline characteristics, 3 842 out of 40 502 gravid patients who delivered within 280 days after Hurricane Harvey's landfall had a significantly higher likelihood of adverse outcomes (maternal morbidity increased by 27% and composite neonatal morbidity increased by 50% after the storm)⁽²⁷⁾. In synthesis, infants from psychologically stressed mothers have less favorable birth outcomes. The father may also be the cause of negative outcomes. In pregnancies where the fathers are 45 years old and over, their offspring have increased psychological and neurocognitive disorders, and childhood cancers⁽²⁸⁾.

ON MENOPAUSE ONSET, CARDIOVASCULAR DISEASE AND OSTEOPOROSIS

The median age at the final menstrual period of women in the US is 52.5 years, with most women becoming menopausal between ages 47 and 54. Sociodemographic factors such as body mass index and education, as well as social stressors, influence this age distribution⁽²⁹⁾. In Latin America, the age at menopause is 49.4 years, and factors associated to an earlier age include higher altitude, low income and lower education⁽³⁰⁾. Ageing modifies the hormones produced by the hypothalamic-pituitary axis, as well as the axis sensitivity to negative feedback by end hormones. Glucose homeostasis tends towards disequilibrium; there is loss of bone,

muscle mass and strength, and an increase in fat mass. Other factors like chronic diseases, inflammation and low nutritional status also affect endocrine systems⁽³¹⁾. In other words, besides ovarian changes, most of the endocrine system becomes less functional with aging, along with immunosenescence, inflammaging and many aging-associated pathologies. Men are aware of the symptoms regularly experienced by their partner; they most frequently identify difficulty in sleeping and lack of energy⁽³²⁾. As for neurovegetative symptoms, a 15-week resistance training program decreases the frequency of moderate and severe hot flushes among postmenopausal women⁽³³⁾, the most feared and fastidious symptom in perimenopause. In general, a moderate level of physical activity has been associated with reduced psychosocial and physical menopause symptoms⁽³⁴⁾.

In a cross-sectional study of 1 367 women with a mean age at menopause of 48.6 years, researchers from Mayo Clinic found that hypertensive diseases of pregnancy may be associated with the severity of menopausal symptoms, specifically somato-vegetative symptoms⁽³⁵⁾. Perimenopausal estradiol fluctuation increases sensitivity to psychosocial stress and vulnerability to depressed mood⁽³⁶⁾. Data from 2 016 women 40 to 80 years old in the Kaiser Permanente Northern California health care system showed that lifetime history of intimate partner violence or sexual assault and current clinically significant symptoms of posttraumatic stress disorder are common, and that these are associated with menopause symptoms⁽³⁷⁾. As violence continues to increase in this part of the world, gynecologists should consider this and the socio-economical background of women (31% of poverty in Latin America and the Caribbean) when evaluating menopausal patients.

Compared with women who had menopause at age 50 to 51, women with premature and early menopause had a substantially increased risk for a non-fatal cardiovascular event before age 60, but not after age 70^(38,39). Early menarche and early menopause seemed to have an exactly additive effect on all-cause mortality⁽⁴⁰⁾.

Hypertensive disorders of pregnancy, including pre-eclampsia, are associated with an increased risk for twelve cardiovascular disorders and chronic hypertension, and the impact is evident



soon after pregnancy⁽⁴¹⁾. In a population-based cohort study of 2.1 million people, preterm birth (gestational age less than 37 weeks) and early-term birth (37 to 38 weeks) were associated with a 53% and 19% increase in the relative risks for ischemic heart disease at ages 30 to 43, respectively, compared with full-term birth (39 to 41 weeks)⁽⁴²⁾. In our region, preeclampsia and prematurity are frequent complications of pregnancy. Women with history of these complications should be advised about preventive measures for cardiovascular disease. Certain types of obesity and higher parity should also be considered in health prevention. In 156 624 postmenopausal women enrolled in the Women's Health Initiative study in the US, normal-weight central obesity was associated with higher risk for all-cause, cardiovascular disease and cancer mortality, compared with normal weight without central obesity^(43,44). Among postmenopausal women at risk for cardiovascular diseases, a higher parity has been associated with higher odds of carotid atherosclerosis, regardless of age, traditional risk factors, anthropometric measures and gestational diseases⁽⁴⁵⁾.

Low-dose aspirin has an established role in the secondary prevention of vascular events (myocardial infarction, ischemic stroke). However, its role in primary prevention is controversial, due to the risks of intracranial hemorrhage⁽⁴⁶⁾.

Hormonal intervention often causes important adverse effects⁽⁴⁷⁾. In developed countries, five years of menopause hormonal treatment (MHT), starting at age 50 years, would increase breast cancer incidence at ages 50 to 69 in about one in every 50 users of estrogen plus daily progestagen preparations, one in every 70 users of estrogen plus intermittent progestagen preparations, and one in every 200 users of estrogen-only preparations. The corresponding excesses from 10 years of MHT would be about twice as great⁽⁴⁸⁾. Nevertheless, commonly prescribed forms of vaginal estrogen with contemporary dosing schedules prevent urinary tract infections (UTI) in postmenopausal women with an active diagnosis of recurrent UTIs⁽⁴⁹⁾. On another note, the only evidence-based indication for prescribing testosterone in women is to treat postmenopausal women diagnosed with hypoactive sexual desire disorder or dysfunction (Level I, Grade A)⁽⁵⁰⁾.

Would a new preventive treatment reduce menopause outcomes along with the need for hormonal treatment? On August 7, 2019, ACOG's Today's Headlines presented a novel procedure that could delay menopause by 20 years. Physicians at ProFam in Birmingham, England, have removed fragments of patients' ovaries to cryogenically freeze them, so that when the woman is approaching the age of menopause, the tissue will be re-implanted, thus "restoring the patient's younger, natural hormones". Technically, it would "delay menopause, osteoporosis, increased heart disease, hot flashes, potential memory problems, and others"⁽⁵¹⁾. There are expectations on this new procedure, as cryopreservation and transplantation of ovarian tissue is already performed for leukemia and other cancers in young women⁽⁵²⁾.

THE BURDEN OF OSTEOPOROSIS

In participants of the National Health and Nutrition Examination Survey, osteoporosis was more prevalent among US adults who were non-citizens, less educated, unemployed, and had a lower income⁽⁵³⁾. Data from 11 020 postmenopausal women from the USA Women's Health Initiative provide evidence for an association between high social stress and greater bone loss throughout six years of follow-up⁽⁵⁴⁾. This relates with the social stressors influencing menopausal age distribution we mentioned earlier. In a sample of 11 084 postmenopausal women from the Women's Health Initiative (WHI), with a mean age of 63.3 years, SD = 7.4, short sleep duration was associated with lower bone mass density and a higher risk for osteoporosis⁽⁵⁵⁾. In the Australian Geelong Osteoporosis Study, higher milk consumption did not increase the risk for major osteoporotic fractures in older women⁽⁵⁶⁾. On the other hand, in a cohort study of 77 206 postmenopausal women with a mean follow-up of 14 years, regular physical activity, including lighter-intensity activities, and less sedentary time are associated with a reduced risk for fracture in older women⁽⁵⁷⁾.

Bisphosphonate and non-bisphosphonate medications for osteoporosis have been significantly associated with decreased mortality after fragility hip fracture^(58,59). Even so, in the UK Clinical Practice Research Datalink, only about one in three patients from 72 256 women receiving os-



teoporosis therapy continued to be in treatment after two years⁽⁶⁰⁾. There is a substantial health care burden of fracture among people under 70 or without osteoporosis, suggesting that focusing on treating people with osteoporosis is unlikely to reduce a large number of fractures in the general population⁽⁶¹⁾. On the other hand, in postmenopausal women, vitamin D supplementation resulted in small but nonsignificant improvements in muscle strength compared with controls⁽⁶²⁾. Among healthy adults, supplementation with higher doses of vitamin D (4 000 IU per day or 10 000 IU per day, compared with 400 IU per day) did not result in improved bone health; further research would be needed to determine whether it is harmful⁽⁶³⁾. In conclusion, we have yet to develop the ideal treatment for osteoporosis.

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