Update in Women's Health: Evidence Published in 2013

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This update summarizes 10 important studies published in 2013 that can change clinical practice. The authors reviewed articles relevant to sex- and gender-based differences in the care of women, defined as research on diseases and conditions more common in women or unique to women and on diseases and conditions in which the approach to care may be different for women. A major theme of research results is the importance of individualizing counseling, screening, and treatment strategies on the basis of patient characteristics.

Breast Cancer

Continuing Adjuvant Tamoxifen Treatment for 10 Years Reduced Recurrence and Increased Survival in Women With Estrogen Receptor–Positive Breast Cancer

Davies C, Pan H, Godwin J, et al; Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) Collaborative Group. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. Lancet. 2013;381:805-16. [PMID: 23219286]

Background: Breast cancer recurrence and death frequently occur more than 5 years after diagnosis. Previous studies of continuing adjuvant treatment with tamoxifen beyond 5 years did not show benefit, but these studies were criticized because of small size and limited follow-up.

According to current guidelines from the American Society of Clinical Oncology, adjuvant treatment with tamoxifen is recommended for premenopausal women with estrogen receptor–positive tumors and for postmenopausal women with estrogen receptor–positive tumors who are unable to tolerate aromatase inhibitors (1).

Findings: In an international trial recruiting patients from Europe, North and South America, Australia and New Zealand, Asia, Africa, and the Middle East between 1996 and 2005, a total of 12 894 women with stage I, II, and III breast cancer who had completed 5 years of tamoxifen treatment were randomly assigned to continue tamoxifen for a total of 10 years or to stop. Among these, 6846 women with estrogen receptor–positive tumors supplied data regarding breast cancer outcomes and adverse effects. The remainder of the women, for whom estrogen receptor status was negative or unknown, had initial analysis for adverse effects only. Average follow-up was 12.6 years after diagnosis.

Women with estrogen receptor–positive disease randomly assigned to 10 years of tamoxifen had a reduced risk for breast cancer recurrence (617 vs. 711 patients; $P = 0.002$), breast cancer mortality (331 vs. 397 patients; $P = 0.01$), and overall mortality (639 vs. 722 patients; $P = 0.01$). The absolute reduction in mortality for women within 5 and 14 years of diagnosis who continued tamoxifen treatment was 2.8 percentage points, with most of the benefit occurring in the period beyond 10 years. Mortality in women without breast cancer recurrence did not differ between the 2 groups (691 vs. 679 patients; relative risk [RR], 0.99; $P = 0.84$). Pulmonary embolism (RR, 1.87 [95% CI, 1.13 to 3.07]) and endometrial cancer (RR, 1.74 [CI, 1.30 to 2.34]) were more common among women randomly assigned to continuation of tamoxifen treatment.

Cautions: Many women initially randomly assigned had undetermined estrogen receptor status and were excluded from analysis of breast cancer outcomes.

Implications: An additional large trial reported in 2013 also showed benefit from continuing tamoxifen treatment for 10 years (2). Continuing tamoxifen therapy should be considered for women who have completed 5 years of therapy. Clinicians should be alert for signs and symptoms of endometrial cancer (such as vaginal bleeding) and venous thromboembolism in women taking tamoxifen. Aromatase inhibitors, with or without sequential tamoxifen, remain the preferred adjuvant endocrine therapy for postmenopausal women (1).

Compared With Biennial Mammography, Annual Mammography Was Associated With Lower Risk for Advanced Cancer and Large Tumors in Women Aged 40 to 49 Years With Extremely Dense Breasts

Kerlikowske K, Zhu W, Hubbard RA, et al; Breast Cancer Surveillance Consortium. Outcomes of screening mammography by frequency, breast density, and postmenopausal hormone therapy. JAMA Intern Med. 2013;173:807-16. [PMID: 23552817]

Background: High breast density is associated with increased risk for breast cancer. The optimal approach to screening women with high breast density is unknown. In the United States, federal law requires that women receive written notification of mammography results. As of September 2013, only 13 U.S. states required that notification include breast density results (3). Breast density is reported using Breast Imaging-Reporting and Data System breast density categories: 1 = almost entirely fat, 2 = scattered fibroglandular densities, 3 = heterogeneously dense, and 4 = extremely dense.

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In 2009, the U.S. Preventive Services Task Force (USPSTF) found convincing evidence that mammography in women aged 40 to 49 years reduced death from breast cancer. However, the overall benefit was deemed to be small, resulting in the recommendation that the decision to start screening mammography before age 50 years should be an individual one and should take patient context into account, including the patient's values regarding specific benefits and harms. Biennial screening was recommended on the basis of evidence of benefit similar to that of annual screening and decreased false-positive results (4, 5).

Findings: In a prospective cohort study, data were collected from 11 474 women with breast cancer and 922 624 women without breast cancer who underwent mammography from radiology facilities in the United States between 1994 and 2008. Compared with annual mammography, biennial mammography for women aged 50 to 74 years was not associated with an increased risk for advanced stage or large tumors, regardless of breast density or menopausal hormone use. Compared with annual mammography, biennial mammography for women aged 40 to 49 years with extremely dense breasts was associated with an increased risk for advanced-stage cancer (odds ratio [OR], 1.89 [CI, 1.06 to 3.39]) and large tumors, defined as tumors greater than 20 mm in diameter (OR, 2.39 [CI, 1.37 to 4.18]). False-positive results were high among women with extremely dense breasts aged 40 to 49 years undergoing annual mammography (65.5% cumulative 10-year risk) and among women with extremely dense breasts who were receiving estrogen plus progestin therapy undergoing annual mammography (65.8% cumulative 10-year risk). The rate of false-positive results was lower among women with fatty breasts aged 50 to 74 years who underwent biennial mammography (17.4% cumulative 10-year risk).

Cautions: Participants were not randomly assigned. The study was not designed to determine the effects of screening on breast cancer mortality and overall mortality.

Implications: This study suggests that women aged 40 to 49 years who choose to undergo mammography and are found to have extremely dense breasts may benefit from annual mammography to reduce diagnoses of advanced disease, at the risk of increased false-positive results. Like all women, women with extremely dense breasts should undergo breast cancer risk evaluation, with genetic testing for women with a family history suggestive of presence of a *BRCA1/2* mutation, and consideration of screening magnetic resonance imaging for women found to have greater than 20% lifetime risk for cancer (6, 7).

Disparities in Survival Between White and Black Medicare Beneficiaries With Breast Cancer Were Mainly Attributable to Differences in Presentation and Comorbid Conditions

Silber JH, Rosenbaum PR, Clark AS, et al. Characteristics associated with differences in survival among black and white women with breast cancer. JAMA. 2013;310:389-97. [PMID: 23917289]

Background: In the United States before 1980, after adjustment for higher incidence among white persons, there were minimal differences in breast cancer mortality between white and black women. Since that time, a significant survival disparity has emerged. The causes of this disparity are not completely understood (8).

Findings: By using the U.S. Surveillance, Epidemiology, and End Results (SEER)–Medicare database, 7375 black women aged 65 years or older diagnosed with breast cancer between 1991 and 2005 were matched with white controls. After adjustment for demographic factors, the 5-year survival rate was 68.8% for white women and 55.9% for black women (difference, 12.9 percentage points [CI, 11.5 to 14.5 percentage points]; $P < 0.001$). Median duration of survival was nearly 3 years shorter for black women. This difference did not significantly change between 1991 and 2005. After adjustment for socioeconomic status, the hazard ratio for breast cancer mortality was no longer significant (1.02 [CI, 0.97 to 1.09]; $P = 0.41$).

Most of the difference in 5-year survival was explained by differences in cancer presentation and comorbid conditions. After adjustment for these factors, the difference in median survival was less than 1 year. Black women received diagnoses of more advanced disease with more adverse biological features. They also had more comorbid conditions and poorer health.

Black women waited longer for treatment (29.2 days vs. 22.5 days; $P < 0.001$), were statistically significantly more likely to have a delay of 3 months or more from diagnosis to treatment (5.8% vs. 2.5%; $P < 0.001$), and were less likely to receive anthracycline and taxane chemotherapy (3.7% vs. 5.0%; $P < 0.001$). They were more likely to receive no treatment except breast-conserving surgery (8.2% vs. 7.3%; $P = 0.04$) or no treatment (12.6% vs. 8.2%; $P < 0.001$).

After matching for demographic characteristics, black women were less likely than white women to have had mammography within the past 6 to 18 months (23.5% vs. 35.7%; $P < 0.001$) and less likely to have evidence of at least 1 primary care visit during the preceding 6 to 18 months (80.5% vs. 88.5%; $P < 0.001$).

Cautions: Endocrine therapies could not be tracked in SEER. Data from SEER could not identify triple-negative tumors, which are more lethal and more common among black women.

Implications: Public health strategies to reduce disparities in breast cancer survival must be comprehensive, targeting the treatment and prevention of comorbid medical conditions, as well as breast cancer screening and treatment. Internists should be aware that black women are at higher risk for adverse breast cancer outcomes and should strive to ensure they receive optimal care, regardless of socioeconomic and insurance status. Some have proposed that disparities in biological characteristics of tumors may be partially attributable to a greater prevalence of occupational

and neighborhood toxic environmental exposures among low-income women. More research is needed (9).

Cervical Cancer Screening

Screening for High-Risk Human Papillomavirus Reduced the Incidence of Cervical Carcinoma Compared With Cytologic Screening Alone

Ronco G, Dillner J, Elfström KM, et al; International HPV Screening Working Group. Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials. Lancet. 2014;383:524-32. [PMID: 24192252]

Background: Screening with cervical cytology and treatment of precursor lesions reduces deaths from cervical cancer and has been standard of care in the developed world for decades. Whether strategies incorporating screening for the presence of high-risk human papillomavirus (HPV) subtypes reduces the incidence of invasive cancer compared with standard cytologic strategies is not known. Because of the high prevalence of HPV in young women, the use of HPV for screening has been recommended only for women aged 30 years or older (10, 11). Testing for HPV is used for risk stratification of atypical squamous cells of undetermined significance in women of all ages (11).

Findings: In 4 randomized, controlled trials in Europe and the United Kingdom, 176 464 women were assigned to liquid-based or conventional cytologic screening according to local guidelines or to HPV testing with or without cytology. In a follow-up study of the original cohorts, median follow-up was 6.5 years. The rate ratio for invasive cervical cancer was 0.60 for women tested with HPV compared with those receiving cytologic testing alone (CI, 0.40 to 0.89). The cumulative incidence of cervical cancer was lower 5.5 years after a negative HPV test result than 3.5 years after a negative cytologic result. Rate ratios were lower for adenocarcinoma (0.31 [CI, 0.14 to 0.69]) than for squamous carcinoma (0.78 [CI, 0.49 to 1.25]). Compared with conventional screening, women randomly assigned to HPV testing were more likely to undergo cervical biopsy (1.35 [CI, 1.30 to 1.40]). This difference was no longer significant when 1 trial that referred HPV-positive women for immediate colposcopy (compared with referring only women with abnormal cytologic results or persistent HPV) was excluded (1.02 [CI, 0.97 to 1.07]).

Cautions: The overall study included multiple protocols that varied according to local practice.

Implications: Current guidelines of the USPSTF, American Cancer Society, and American College of Obstetricians and Gynecologists recommend cervical cancer screening every 3 years starting at age 21 years, with optional addition of HPV screening for women aged 30 years or older. For women with negative cytologic and negative HPV testing results, a 5-year screening interval is recommended (10, 11). This study suggests that the addition of HPV testing reduces the incidence of invasive cervical cancer by increasing identification of precursor lesions for cervical adenocarcinoma.

Menopause

Menopausal Hormone Therapy Should Not Be Used for Chronic Disease Prevention but Is Appropriate for Symptom Management in Some Women

Manson JE, Chlebowski RT, Stefanick ML, et al. Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. JAMA. 2013;310:1353-68. [PMID: 24084921]

Background: The Women's Health Initiative, funded by the National Institutes of Health in 1991, included randomized trials of hormone therapy for chronic disease prevention. The initial and ongoing results of these trials led to guidelines recommending against the use of menopausal hormone therapy to prevent chronic diseases. Controversy about these findings persisted, leading to continued interest in following the cohorts after the trials and interventions were stopped.

Findings: A total of 16 608 postmenopausal women with an intact uterus were randomly assigned to conjugated equine estrogen (CEE), 0.625 mg/d, and medroxyprogesterone acetate (MPA), 2.5 mg/d, or to placebo. A total of 10 739 women who had undergone hysterectomy were randomly assigned to CEE, 0.625 mg/d, or placebo. Median duration of intervention was 5.6 years in the CEE plus MPA trial and 7.2 years in the CEE-alone trial, with 13 years of follow-up, including the intervention phase. Both trials were stopped early because benefits did not exceed risks. Risks of CEE plus MPA during intervention included invasive breast cancer, stroke, pulmonary embolism, dementia (in women aged 65 years or older), gallbladder disease, and urinary incontinence. Benefits included decreased hip fractures and diabetes. Most risks and benefits did not persist after hormone treatment was stopped, except for an elevation in breast cancer risk during cumulative follow-up (434 cases vs. 323 cases; hazard ratio, 1.28 [CI, 1.11 to 1.48]). Risks of CEE only did not include invasive breast cancer, but risks and benefits were otherwise similar to those in the CEE plus MPA group. Absolute risks of adverse events per 10 000 women taking CEE plus MPA differed by age, ranging from 12 excess cases for women aged 50 to 69 years to 38 excess cases for women aged 70 to 79 years. For CEE alone, the range was 19 fewer cases for women aged 50 to 59 years to 51 excess cases aged 70 to 79 years.

Cautions: The mean age of women in the Women's Health Initiative was 63 years. Most women in clinical practice start hormone therapy at the time of menopause.

Implications: The effects of menopausal hormone therapy on chronic disease are complex. The USPSTF and the American College of Obstetricians and Gynecologists recommend against the use of menopausal hormone therapy for prevention of chronic disease (12, 13). Hormone therapy remains the most effective treatment for vasomotor symptoms. Menopausal hormone therapy should be used at the lowest dose for the shortest period needed for symptom control, and women should be fully informed of risks and benefits.

Menorrhagia

Levonorgestrel-Containing Intrauterine Device Was More Effective Than Other Commonly Used Medical Treatments to Reduce Bleeding Symptoms and Improve Quality of Life in Patients With Menorrhagia But Did Not Reduce Surgical Interventions

Gupta J, Kai J, Middleton L, et al; ECLIPSE Trial Collaborative Group. Levonorgestrel intrauterine system versus medical therapy for menorrhagia. N Engl J Med. 2013;368:128-37. [PMID: 23301731]

Background: Menorrhagia interferes with quality of life and is a leading indication for surgical procedures in women of reproductive age, including endometrial ablation and hysterectomy. Since 2009, the levonorgestrel intrauterine system (IUS) has been approved by the U.S. Food and Drug Administration for treatment of heavy menstrual bleeding among women who choose to use an intrauterine device for contraception (14). Risks and benefits of the levonorgestrel IUS for menorrhagia compared with those of other nonsurgical options had not been systematically studied.

Findings: In a study performed in the United Kingdom, 571 women were randomly assigned to usual care (mefenamic acid [a nonsteroidal anti-inflammatory drug]; tranexamic acid [an antifibrinolytic agent]; or combined estrogen–progestin or progestin alone, at their clinician's discretion) or levonorgestrel IUS. At 2 years, improvement in the Menorrhagia Multi-Attribute Scale (MMAS) was greater for the levonorgestrel IUS group than the usual care group (mean difference in improvement, 13.4 points on a scale of 100 points [CI, 9.9 to 16.9]; $P < 0.001$), and more women were still using the levonorgestrel IUS at 2 years compared with other methods (64% vs. 38%; $P < 0.001$). Benefit was greatest for levonorgestrel IUS compared with usual care for women with a body mass index (BMI) greater than 25 kg/m^2; this was attributed to less effectiveness of alternative treatments for overweight and obese women (MMAS score, 16.7 [CI, 12.6 to 20.9; $P < 0.001$] vs. 5.4 [CI −1.0 to 11.8; $P = 0.10$]) Rates of surgical intervention, sexual activity scores, and major adverse events did not significantly differ between the 2 groups.

Cautions: Levonorgestrel IUS was not compared individually with other nonsurgical options. Nonsurgical options were at the discretion of individual clinicians. Many women switched treatments over the 2-year study. The study was not powered to detect differences in rare adverse events.

Implications: In patients presenting with menorrhagia, levonorgestrel IUS results in improved quality of life compared with usual care, defined as one or more other medical options prescribed by clinicians, but does not reduce surgical interventions. Insertion of the levonorgestrel IUS device is an invasive procedure, and the cost of the device can be a barrier for some patients. Patients and clinicians should consider these factors when deciding on treatments for menorrhagia.

Osteoporosis

Repeating Bone Mineral Density Testing After 4 Years in Older Adults Did Not Improve Prediction of Hip or Major Osteoporotic Fracture

Berry SD, Samelson EJ, Pencina MJ, et al. Repeat bone mineral density screening and prediction of hip and major osteoporotic fracture. JAMA. 2013;310:1256-62. [PMID: 24065012]

Background: The USPSTF recommends bone mineral density (BMD) screening for all women at age 65 years and for younger postmenopausal women with additional risk factors for osteoporotic fracture (15). Optimal strategies for rescreening are not clear.

Findings: Surviving members of the Framingham cohort study were invited for 3 BMD measurements obtained approximately 4 years apart. Study participants were 492 women and 310 men (mean age, 75 years) who had not had a hip fracture and underwent 2 measurements of femoral neck BMD between 1987 and 1999. The area under the curve for prediction of hip or major osteoporotic fractures was 0.71 (CI, 0.62 to 0.75) for a model incorporating only baseline BMD, compared with 0.68 (CI, 0.62 to 0.75) for a model incorporating BMD change on the basis of repeating a BMD measurement within 4 years. High risk for fracture was defined as 3% or greater and 20% or greater 10-year risk for hip and major osteoporotic fracture, respectively. Compared with baseline BMD measurement alone, a second BMD identified as high risk an additional 3.9% (CI, −2.2% to 9.9%) of participants who experienced hip fracture, and an additional and 9.7% (CI, 3.4% to 15.7%) of participants who experienced a major osteoporotic fracture.

Cautions: All participants were white. Most participants had measurements on 2 different machines. Because precision error can affect the accuracy of results, measurement on the same machine is generally recommended when possible. Except for estrogen, use of drugs that reduce osteo-

porotic fracture risk was not collected. Family history of hip fracture was not collected. Follow-up after the second BMD measurement was 9.6 years.

Implications: Medicare pays for bone density screening for women with osteopenia every 2 years, and some insurers in the United States have programs to encourage this screening frequency. Studies now suggest that for most patients, intervals longer than 2 years are as predictive as more frequent measurement. In the Study of Osteoporotic Fractures, in women aged 67 years or older, the intervals that captured 90% of women developing osteoporosis by BMD criteria (T-score, −2.5 or lower) were calculated to be 15 years for women with a baseline normal BMD or T-score of −1.01 to −1.49, 5 years for women with a baseline T-score of −1.50 to −1.99, and 1 year for women with a baseline T-score of −2.00 to −2.49 (15, 16).

Ovarian Cancer

Use of Oral Contraceptives Is Associated With a Lower Risk for Ovarian Cancer in *BRCA1/2* Carriers

Moorman PG, Havrilesky LJ, Gierisch JM, et al. Oral contraceptives and risk of ovarian cancer and breast cancer among high-risk women: a systematic review and meta-analysis. J Clin Oncol. 2013;31:4188-98. [PMID: 24145348]

Background: Women from families with multiple cases of breast or ovarian cancer who are found to have a *BRCA1* or *BRCA2* mutation are at very high risk for ovarian cancer. In a study of *BRCA1/2* mutation carriers, lifetime risk for ovarian cancer was 54% for *BRCA1* and 23% for *BRCA2* carriers. Risk was 2% to 3% by age 40 years, increasing to 21% by age 50 years for *BRCA1* carriers (17).

In cohort studies, salpingo-oophorectomy in *BRCA1/2* carriers is associated with lower breast cancer–specific and ovarian cancer–specific mortality. Overall, salpingo-oophorectomy has been associated with a 60% reduction in all-cause mortality in *BRCA1/2* carriers (18).

Oral contraceptive use is associated with decreased ovarian cancer risk in the general population. The risks and benefits of oral contraceptive use in women at high risk for ovarian cancer are uncertain.

Findings: A meta-analysis of 6 studies of ovarian cancer risk and 8 studies of breast cancer risk in *BRCA1/2* mutation carriers was performed. Oral contraceptive use was associated with a statistically significant decreased risk for ovarian cancer (OR, 0.58 [CI, 0.46 to 0.73]) and a nonsignificant trend to increased risk for breast cancer (OR, 1.21 [CI, 0.93 to 1.58]).

Cautions: Studies were not randomized. Effects of duration and timing of use could not be analyzed. Type and dose of oral contraceptive were not reported. Whether associations varied according to specific *BRCA1/2* mutations could not be determined. Some studies examined only prevalent cases, possibly introducing bias if cases related to oral contraceptive use were more aggressive, and patients died before they could be included.

Implications: Risk-reducing salpingo-oophorectomy should be offered to all *BRCA1/2* carriers. For young women who wish to delay salpingo-oophorectomy, or for premenopausal women who decline it, use of oral contraceptives may be considered for contraception. Data are insufficient to recommend them for risk reduction. Oral contraceptives should be offered only to *BRCA1/2* carriers who are fully counseled on risks and benefits, including risks of delaying or declining risk-reducing surgery.

Reproductive Health

Maternal Use of Valproic Acid During Pregnancy Was Associated With an Increased Risk for Autism in Offspring

Christensen J, Grønborg TK, Sørensen MJ, et al. Prenatal valproate exposure and risk of autism spectrum disorders and childhood autism. JAMA. 2013;309:1696-703. [PMID: 23613074]

Background: Exposure to antiseizure medications during fetal life has been associated with congenital malformations and delayed cognitive development. Case series and animal models have suggested that prenatal exposure to valproic acid may increase the risk for autism.

Findings: Danish researchers used data from comprehensive national databases to estimate the risk for autism for children whose mothers filled prescriptions for valproic acid during pregnancy. Among more than 650 000 births in Denmark between 1996 and 2006, children with autism spectrum disorder were identified. Mean age of children at end of follow-up was 8.8 years. Compared with children not exposed to valproic acid, those exposed to valproic acid had a 4.42% absolute risk for autism spectrum disorder (adjusted hazard ratio, 2.9 [CI, 1.7 to 4.9]) and a 2.5% risk for childhood autism (adjusted hazard ratio, 5.2 [CI, 2.7 to 10.0]). In comparison, the risks for autism spectrum disorder and childhood autism among offspring of epileptic women not exposed to valproate were 2.44% (CI, 1.88% to 3.16%) and 1.02% (CI, 0.70% to 1.49%), respectively.

Cautions: Researchers did not have complete information about use of folate, alcohol, or illicit drugs during pregnancy. Information about parental psychiatric disorders was incomplete. The study did not measure drug adherence or drug levels during pregnancy. Race and ethnicity were not reported, but participants were presumably primarily white Europeans.

Implications: Approximately 925 000 U.S. women of reproductive age fill prescriptions for valproic acid annually. Most of these prescriptions are for treatment not of epilepsy but of other conditions, such as bipolar disorder and migraine headache (19). In 2013, the U.S. Food and Drug Administration changed the designation of valproic acid to pregnancy category X (risks of use in pregnant women

clearly outweigh benefits) for migraine headache. It remains category D (the potential benefit of the drug in pregnant women may be acceptable despite its potential risks) for treatment of epilepsy and manic episodes in women with bipolar disorder (20). Because half of pregnancies are unplanned, all women of childbearing potential should be counseled about teratogenic effects when they are prescribed valproic acid. Women who require treatment with antiseizure drugs who may become pregnant should be treated with drugs other than valproic acid when possible.

Women With a History of Bariatric Surgery Are at Increased Risk for Preterm and Small-for-Gestational-Age Birth

Roos N, Neovius M, Cnattingius S, et al. Perinatal outcomes after bariatric surgery: nationwide population based matched cohort study. BMJ. 2013;347:f6460. [PMID: 24222480]

Background: The effect of bariatric surgery on subsequent birth outcomes is unknown. Higher BMI increases the risk for preterm birth, including extremely preterm birth, a leading cause of infant death (21). Bariatric surgery decreases BMI and thus may result in overall reduced risk in an individual woman. Bariatric surgery is associated with a lower risk for large-for-gestational-age birth. (22). Earlier studies suggested that birth outcomes were as good as or better than those in matched controls, but these studies were limited by small size (23). However, more recent studies have raised concerns about some possible negative outcomes (22).

Findings: Swedish researchers used a comprehensive national database of 1 742 702 singleton births to identify 2562 births to women with a history of bariatric surgery from 1992 and 2009. Control births were matched by maternal age, parity, early pregnancy BMI, smoking status, educational level, and year of delivery. Compared with controls, women with a history of bariatric surgery were more likely to have small-for-gestational-age birth (5.2% vs. 3.0%; OR, 2.0 [CI, 1.5 to 2.5]; $P < 0.001$), spontaneous premature birth (5.2% vs. 3.6%; OR, 1.5 [CI, 1.2 to 1.9]; $P < 0.001$), and medically indicated preterm birth (4.5% vs. 2.5%; OR, 1.8 [CI, 1.4 to 2.3]; $P < 0.001$). The differences in preterm birth were observed only in women with a BMI less than 35 kg/m^2. Women with a history of bariatric surgery had a lower risk for large-for-gestational-age birth (4.2% vs. 7.3%; OR, 0.6 [CI, 0.4 to 0.7]; $P < 0.001$). There were no differences in stillbirth or neonatal death. Results did not vary according to procedure type; in Sweden, gastric bypass became a more common procedure over time compared with vertical banded gastroplasty.

Cautions: Presurgery weight and weight loss between surgery and pregnancy were unavailable. Not all bariatric surgeries were captured. Race and ethnicity were not reported, but participants were presumably primarily white Europeans.

Implications: Counseling women considering bariatric surgery who may become pregnant afterward is complex. Multiple health benefits for the woman and potential offspring must be considered. However, women should be informed that, for unclear reasons, bariatric surgery may confer risk for preterm birth and small-for-gestational-age birth, among other risks.

The importance of obstetric care, including preconception counseling, should be emphasized. Gastric bypass in particular can cause multiple micronutrient deficiencies. Although mechanisms for adverse outcomes associated with bariatric surgery are unknown, it is prudent to advise women who have had bariatric surgery and may become pregnant of the importance of maintaining micronutrient intake before conception and during pregnancy.

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