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Evidence-based commentaries on women's reproductive health

ABSTRACT & COMMENTARY

Paternal Age Is Important for Perinatal Outcomes

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Dr. Rebar reports no financial relationships to this field of study.

SYNOPSIS: Fathering infants at or after age 45 years is associated with negative effects on both the mothers and the resulting offspring.

SOURCE: Khandwala YS, Baker VL, Shaw GM, et al. Association of paternal age with perinatal outcomes between 2007 and 2016 in the United States: Population based cohort study. *BMJ* 2018;363:k4372. doi: 10.1136/bmj.k4372.

To assess the effect of paternal age on maternal and perinatal outcomes, investigators conducted a retrospective cohort analysis of all live births between 2007 and 2016 within the United States as published by 30.0 years to 31.2 years. After adjustment for a variety of factors, including maternal age, race, education, smoking status, and number of prenatal visits, births related to the oldest fathers were associated with worse outcomes. Children born to fathers older than 45 years of age had a 14% higher chance of preterm birth (< 37 weeks) compared with fathers between 25 and 34 years of age (adjusted odds ratio [aOR], 1.14; 99% confidence interval [CI], 1.13-1.15). Children born to fathers 45 to 54 years of age had a 14% higher risk of low birth weight (< 2,500 g) than children born to younger fathers (aOR, 1.14; 99% CI, 1.12-1.15). Fathers older than 45 years of age had 28% increased odds of a pregnancy complicated by gestational diabetes compared with fathers aged 25 to 34 years (aOR 1.28; 99% CI, 1.27-1.30). After stratification by maternal age, increasing paternal age remained significantly associated with perinatal outcomes. In addition, the findings were similar when the analysis was limited to first births for mothers.

■ COMMENTARY

Although the authors of this extraordinarily large and robust study documented only a modest effect

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of advanced paternal age (> 45 years) on perinatal outcomes, the effect is of great significance because the percentage of all U.S. births to fathers older than 40 years of age has doubled to approximately 9% since the 1970s.[1] Khandwala et al estimated the population-attributable risk of advanced paternal age by recalculating the distribution of paternal age groups for a postulated scenario in which all fathers were younger than 45 years of age. During the past 10 years, 13.2% (95% CI, 12.5-13.9%) of premature births and 14.5% (95% CI, 13.6-15.4%) of low birth weight infants with older fathers can be attributed to the increase in fathers older than 45 years of age. In addition, 15.1% (95% CI, 14.2-15.9%) of neonatal intensive care unit admissions and 18.2% (95% CI, 17.5-18.9%) of gestational diabetes diagnoses were attributable to the increase in older fathers.

In contrast to older mothers, it has been difficult to estimate any effect of advanced paternal age on offspring. Gradually, it has become recognized that the offspring of fathers with advanced paternal age (defined in most reports as older than 50 years of age) have increased rates of genetic abnormalities, cancer, autism, and other psychiatric disorders.[2,3] Still, any reported changes develop gradually without any specific age cutoff.

In women, regardless of their age, 23 cell divisions are required to form mature egg cells from oogonia. In men, about 30 spermatogonial cell divisions occur before puberty.[3] After puberty, spermatogonial cells divide about 23 times per year. For example, sperm produced by a 70-year-old male will have formed after perhaps 1,300 spermatogonial mitotic divisions. Thus, it is not difficult to deduce that advanced paternal age may lead to an increased number of de novo mutations.

In 2012, Kong et al reported on whole genome sequencing of parents and children from 78 Icelandic families.[4] The researchers convincingly documented an association between paternal age at conception and the frequency of de novo mutations in offspring across the entire genome. This association was significant, especially for genes associated with autism spectrum disorders.[4] As a result of this seminal study, it has become firmly established that advanced paternal age can contribute to birth defects associated with single gene mutations and chromosomal abnormalities. Both bipolar disorders and schizophrenia also have been linked to advanced paternal age.[5,6]

Achondroplasia, the most common cause of dwarfism, was the first genetic disorder thought to be influenced by paternal age.[7] This autosomal dominant disorder now is known to be caused by mutations in the fibroblast growth factor 3 (FGFR3) gene.[8] Similarly, mutations in the FGFR2 gene, which lead to autosomal dominant craniosynostotic disorders, also are associated with paternal age.[9] Mutation in the RET gene, which leads to multiple endocrine neoplasia, is another example of a genetic disorder that almost exclusively has paternal origin associated with paternal age.[3]

With regard to chromosomal aberrations, researchers now recognize that the extra chromosome 21 is of paternal origin in approximately 10% of Down syndrome cases. Advanced paternal age significantly affects the incidence of Down syndrome when the female partner is older than 35 years of age.[10] Furthermore, although controversial, it has been suggested that 50% of cases of Klinefelter syndrome with a 47,XXY karyotype are attributable to the male.[11]

Advanced paternal age also appears to have an association with malignant disease. In an extremely large cohort study from Northern Ireland, researchers found a small but significant increase in the risk of leukemia in children of fathers of advanced paternal age.[12] A population-based cohort study from Sweden corroborated this increased risk of leukemia and also found an effect of paternal age on the incidence of central nervous system cancers.[13] Even when controlling for maternal age, breast cancer also was associated with advanced paternal age, and the effect appeared to be stronger for breast cancer arising in premenopausal women.[14]

Thus, the Khandwala et al study adds to our knowledge about the effect of advanced paternal age on the offspring. The authors suggested that epigenetic changes in the sperm of older men may affect placental and embryonic growth and account for the preterm delivery, low birth weight, and low Apgar scores

observed.[15] Together with the genetic studies discussed, the current data indicate the need to counsel couples about the risks involved when the father is older. The risks not only are genetic but also involve other neonatal outcomes as well. Guidelines established by the American College of Genetics indicate that genetic testing for any pregnancy involving a man with advanced paternal age should be treated similarly to any other pregnancy.[16] ■

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ABSTRACT & COMMENTARY

Does Treatment of Bacterial Vaginosis Prevent Spontaneous Preterm Birth?

By Rebecca H. Allen, MD, MPH

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Dr. Allen reports she receives grant/research support from Bayer and is a consultant for Merck.

SYNOPSIS: In this randomized, controlled trial from France, screening for and treatment of bacterial vaginosis in pregnant women at low risk for preterm birth with oral clindamycin or placebo did not reduce the rate of spontaneous preterm birth between 16 and 36 weeks.

SOURCE: Subtil D, Brabant G, Tilloy E, et al. Early clindamycin for bacterial vaginosis in pregnancy (PREMEVA): A multicentre, double-blind, randomised controlled trial. *Lancet* 2018;392:2171-2179.

This randomized, double-blind, placebo-controlled trial was conducted at 40 centers in France between 2006 and 2011. Researchers screened adult women for bacterial vaginosis (BV) during the first trimester of pregnancy. Self-collected samples were sent to the laboratory for Gram staining, and Nugent scores were calculated (7 or higher defined BV). Women with BV, no history of second trimester pregnancy loss (16 to 21 6/7 weeks), and no history of preterm delivery (22 to 36 6/7 weeks) were invited to participate in the trial. Exclusion criteria included gestational age 15 weeks or greater, allergy to clindamycin, vaginal bleeding within the week of screening for BV, or planning to deliver in a different region of France. Participants were assigned randomly to either a single-course clindamycin (300 mg orally twice a day for four days × 1 with placebo for the remaining two months), triple-course clindamycin (300 mg orally twice a day for four days every month for three months), or placebo for three months. Women with BV at high risk for preterm delivery (history of second trimester pregnancy loss or preterm delivery) were offered participation in a subtrial and were randomized to either single-course clindamycin or triple-course clindamycin without a placebo arm. The primary outcome was the rate of spontaneous delivery between 16 and 32 weeks.

A total of 2,869 women were assigned randomly to groups in the low-risk trial (943 single-course

clindamycin, 968 triple-course clindamycin, and 958 placebo) and 236 in the high-risk trial (122 single-course, 114 triple-course). Half of the participants were nulliparous, and the median gestational age at randomization was 12 4/7 weeks. Ninety-five percent of women began treatment before 15 weeks' gestation. A total of 1.2% of women in the clindamycin group and 1.0% of women in the placebo group delivered spontaneously between 16 and 32 weeks ($P = 0.82$). Preterm delivery between 22 and 36 6/7 weeks also was similar between the groups (4.8% vs. 4.1%; $P = 0.40$). A repeat analysis measuring compliance with the regimen by counting pills showed no difference. The most common adverse event in the clindamycin group was diarrhea (1.6%). The high-risk subtrial also showed no differences in preterm delivery between 16 and 32 weeks with the two regimens of clindamycin (triple-course 4.4% vs. single-course 6.6%; $P = 0.47$), but there was no placebo arm.

[For now, it is clear that although symptomatic pregnant women with bacterial vaginosis should be diagnosed and treated, there is no evidence for screening and treating asymptomatic pregnant women.]

■ COMMENTARY

BV occurs when the vaginal microbiome is disrupted with an overgrowth of anaerobic bacteria (*Gardnerella vaginalis* and other species) and an absence of vaginal lactobacilli.[1] BV can be diagnosed with a Gram stain of vaginal flora (Nugent score), a wet prep to evaluate for clue cells, elevated vaginal pH and a positive whiff test, or a DNA probe assay for detecting *G. vaginalis* when present at a high concentration. BV now is recognized as a biofilm infection, and it has been found that this biofilm can ascend into the uterine cavity.[1] This may explain the association of BV with adverse outcomes such as preterm birth, chorioamnionitis, endometritis after delivery or abortion, and pelvic inflammatory disease.

The relationship between BV and preterm birth has been well documented. Previous meta-analyses have shown an association between BV and preterm birth before 37 weeks, especially when BV was present early in gestation.[2] Researchers surmise that ascending bacteria early in pregnancy could predispose certain patients to preterm birth. However, several studies and meta-analyses on screening for and treatment of BV in pregnant women at low risk for preterm delivery have yielded conflicting results.[3] Similarly, in pregnant women at high risk for preterm delivery, screening for and treatment of BV has been controversial.[1] The Centers for Disease Control and Prevention (CDC) currently states, "Evidence is insufficient to recommend routine screening for BV in asymptomatic pregnant women at high or low risk for preterm delivery for the prevention of preterm birth."[3]

Subtil et al wanted to perform a large trial to finally answer the question about the utility of this intervention in pregnant women at low risk for preterm birth. The study has several strengths, including the large sample size, objective criteria for diagnosis of BV, and randomization. It is not clear how the authors determined which BV treatment regimen to use. Oral clindamycin 300 mg twice daily for four days is not a regimen endorsed by the CDC in the United States, but perhaps it is common in France. The CDC classifies oral clindamycin 300 mg twice daily for seven days as an alternative regimen, not a preferred one. Nevertheless, the authors of previous trials of clindamycin for preterm birth used the same dosing for five days and showed eradication of BV in more than 90% of cases.

The study clearly showed no benefit for low-risk women. Interestingly, for the high-risk group that participated in the subtrial, the authors noted that French ethics guidelines prevented them from including a placebo arm. Unfortunately, the lack of the placebo arm prevents us from drawing any conclusions about the efficacy of the intervention in preventing preterm birth in that population. I do not think that including a placebo arm would have been unethical given the uncertainty of the benefits of the intervention. More research is needed to elucidate which populations of women should be screened and treated for BV in pregnancy to prevent adverse sequelae. There may be a genetic component that increases susceptibility to BV-associated preterm birth that we have not yet elucidated. For now, however, it is clear that although symptomatic pregnant women with BV should be diagnosed and treated, there is no evidence for screening and treating asymptomatic pregnant women. ■

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ABSTRACT & COMMENTARY

Low-Dose Aspirin and Preterm Birth

By John C. Hobbins, MD

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Dr. Hobbins reports no financial relationships relevant to this field of study.

SYNOPSIS: A reanalysis of an earlier randomized clinical trial to assess the ability of low-dose aspirin to prevent preeclampsia has shown that the drug diminishes the risk of spontaneously delivering prior to 34 weeks by about half.

SOURCE: Andrikopoulou M, Purisch SE, Handal-Orefice R, Gyamfi-Bannerman C. Low-dose aspirin is associated with reduced spontaneous preterm birth in nulliparous women. *Am J Obstet Gynecol* 2018;219:399.e1-399.e6.

Many previous Alerts have included reviews of methods to diminish the rates of spontaneous preterm birth (PTB) and preeclampsia. Now, a study emerges that resurrects data from an earlier randomized, clinical trial (RCT) by Sibai et al that addressed the ability of low-dose aspirin (ASA) to prevent preeclampsia.[1] However, this time, Andrikopoulou et al crossed over to study the drug's ability to diminish the rate of PTB. A well-documented feature of preeclampsia — a failure of deep (myometrial) trophoblastic invasion of the spiral arteries — has been implicated as a possible cause of PTB.[2] This link has not been given the attention it deserved because of the more obvious tendency to blame preeclampsia-related PTB on the frequent need to intervene early. Also, in recent years the focus in spontaneous PTB has been on infection and cytokine-generated inflammation.

In 1993, Sibai et al explored the ability of low-dose ASA to prevent preeclampsia in nulliparous pregnant women.[1] The preventive results were underwhelming, and the data languished until a group from New York decided to study what was not addressed in the earlier study: low-dose ASA and its relationship to spontaneous PTB. Through the National Institutes of Health Maternal-Fetal Medicine Network, 2,543 women from seven centers were enrolled between 1989 and 1991. Half were given 60 mg ASA per day and the other half received placebo, with administration between 13 and 25 weeks of gestation. The primary outcome was spontaneous PTB < 34 weeks, and the secondary outcomes were spontaneous PTB < 37 weeks, overall PTB at < 34 weeks and < 37 weeks, and the incidence of abruption and/or any type of hemorrhage.

There was a statistically significant difference between ASA and placebo in the primary outcome variable: the rate of PTB < 34 weeks (1.03% vs. 2.34%; odds ratio [OR], 0.43; 95% confidence interval [CI], 0.26-0.84). Differences in the rates of PTB < 37 weeks (7.03% vs. 6.58%; OR, 1.04; 95% CI, 0.78-1.39), as well as those for PTB for any reason at < 37 weeks and at < 34 weeks, were not significant between the ASA and placebo groups. Also, there was no evidence of increased rates of hemorrhage with ASA.

Importantly, reductions in PTB < 34 weeks remained significant after adjusting for many confounding variables. Since there are some data to suggest that ASA works best when administered prior to 16 weeks,[3] the authors addressed this issue. They found that ASA after 16 weeks yielded a similar doubling in the reduction of PTB < 34 weeks (OR, 2.17; 95% CI, 1.05-4.45).

[Should every pregnant patient take aspirin? When confronted with a question like this that is so 'out there,' we always counter with 'it needs more investigation.' In this case … that response sounds right.]

Of all the variables tested, there was only one other significant difference between the study groups: a higher rate of placental abruption (0.72% vs. 0.08%; OR, 10.0; 95% CI, 1.16-100) in the ASA cohort. This finding also received some initial attention when the original study was published.[1] However, since the placebo group had an unfairly low incidence of abruption (zero), and the rate of abruption in the ASA group was the same as historical controls, this relationship has been downplayed substantially.

■ COMMENTARY

Every few years, another reason to use ASA surfaces. Most studies do show a benefit of ASA to prevent preeclampsia, especially in high-risk patients. In addition, cardiologists have hyped its ability to prevent strokes and cardiovascular events in at-risk patients and have recommended its use in others,

seemingly for no reason other than being old. ASA discourages platelet aggregation and appears to have a beneficial effect on spiral artery remodeling in the placental bed. It certainly has anti-inflammatory properties. It is inexpensive and has few side effects in those with normal clotting function.

Now, we find that it may decrease PTB at a time when prematurity exerts its greatest morbidity (< 34 weeks), even in those with no risk factors. Does this mean that every pregnant patient should take it? When confronted with a suggestion like this that is so "out there," we always counter with "it needs more investigation." In this case, based on the nature of the study and that this was the only real finding that was significant, that response sounds about right. ■

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ABSTRACT & COMMENTARY

Pregnancy Temporarily Increases Breast Cancer Risk: Parallels to Hormonal Contraception?

By Jeffrey T. Jensen, MD, MPH

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Dr. Jensen reports he receives grant/research support from and is a consultant for ObstetRx, Bayer, Merck, and Sebela Pharma; is a consultant for AbbVie, Mithra, and Daré Bioscience; and receives grant/research support from CooperSurgical and Population Council.

SYNOPSIS: In a pooled analysis of prospective studies, researchers found an increased risk of breast cancer among parous women that persists for more than 20 years after childbirth. Breastfeeding did not modify this pattern.

SOURCE: Nichols HB, Schoemaker MJ, Cai J, et al. Breast cancer risk after recent childbirth: A pooled analysis of 15 prospective studies. *Ann Intern Med* 2018; Dec 11. doi: 10.7326/M18-1323. [Epub ahead of print].

In prior research evaluating the association of parity to breast cancer risk, investigators have found an increased risk during and shortly after giving birth, followed by protection. Although the increase in risk following pregnancy persists for several years, the roles of breastfeeding, family history, and specific tumor types remain controversial. To better define these relationships, the research team led by Nichols and Schoemaker used data from the Premenopausal Breast Cancer Collaborative Group, a pooling project involving 20 prospective cohort studies.[1] The authors of the participating studies followed women without breast cancer younger than 55 years of age through direct contact or linkage with cancer registries. All the studies provided information on important confounders such as age, demographic characteristics, lifestyle factors, reproductive history, medical conditions, and first-degree family history of breast cancer. From this group of studies, the authors identified 15 cohorts that provided information on women's ages at childbirth and pooled these results for a reanalysis. Information about breastfeeding status was available in 12 studies, family history in 12 studies, and tumor stage or estrogen receptor status in 13 studies.

The investigators used Cox proportional hazards regression to calculate hazard ratios (HRs) and 95% confidence intervals [CIs] for the association between time since most recent birth and breast cancer, using attained age as the underlying time scale. They adjusted these HRs for age at first birth, parity, and breastfeeding. They considered first-degree family history an effect modifier, and conducted separate analyses for positive and negative family history. The pooled results included 889,944 women who contributed 9,625,727 person-years of follow-up (mean,10.8 years; standard deviation, 6.4 years). At enrollment, 81% of the cohort were parous and an additional 8% gave birth during follow-up. The mean age at study entry was 41.8 years (range, 16.0-54.9 years). Overall, women who reported a family history of breast cancer contributed 12.4% of person-years of follow-up. Among parous women,

women who reported breastfeeding contributed 72.9% of the person-years.

Compared with nulliparous women, the overall HR for breast cancer among parous women peaked 4.6 years after the most recent birth (HR, 1.80; 95% CI, 1.63-1.99). The point estimate of risk did not change from elevated to reduced until 23.6 years (CI, 21.9-25.0) after birth, decreasing to its lowest observed point (HR, 0.77; 95% CI, 0.67-0.88) 34.5 years after birth. Although the effect of a positive family history only modestly increased the risk of breast cancer among parous women (HR, 1.82; 95% CI, 1.48-2.24 at 4.9 years), the risk increased substantially (HR, 3.53; 95% CI, 2.91-4.29 at 4.9 years) using a comparison group that only included nulliparous women without a family history.

The age of first birth influenced the pattern of risk. The authors found no increased risk among women who had their first birth before age 25 years (HR, 1.06; 95% CI, 0.67-1.66 at < 1 year), but weak associations for those with first births at 25-34 years of age (HR, 1.25; 95% CI, 1.11-1.40 at 4.6 years) and 35-39 years of age (HR, 1.40; 95% CI, 1.14-1.72 at 6.4 years). In contrast, breastfeeding history did not change the overall patterns.

Tumor type only modestly influenced risk patterns for parous women relative to nulliparous. The peak HR for estrogen receptor-positive breast cancer (HR, 1.88; 95% CI, 1.62-2.20 at 5.3 years after most recent birth) crossed the null value at 25.0 years (HR, 0.90; 95% CI, 0.74-1.09). For estrogen receptor-negative breast cancer, the HR peaked at 2.2 years after birth (HR, 1.77; 95% CI, 1.34-2.33), but never crossed over to protection (HR, 1.38; 95% CI, 1.01-1.88 even 34.5 years after birth).

■ COMMENTARY

Nichols et al combined individual-level data from almost 1 million women collected from 15 prospective cohort studies to investigate breast cancer risk in reproductive-aged women. They found that compared to nulliparous women, parous women had an elevated breast cancer risk that peaked around five years after childbirth and lasted about 20 years. The persistence of the elevation of risk and the absence of a protective effect from breastfeeding represent novel findings. The pooling of results from several prospective studies provides a large number of subjects with incidence data on breast cancer, allowing for the calculation of hazard ratios. A notable strength is the availability of data on the number and timing of pregnancy. Breastfeeding history was available in only 12 of the 15 cohorts, making these conclusions less reliable. The large number of subjects provides sufficient statistical power to yield tight confidence intervals around the HRs. However, it is important to note that the point estimates for most of the HRs reported are under 2.0, suggesting weak associations. Although the investigators made careful and transparent efforts to reduce bias by considering potential confounders and effect modifiers, these factors were not collected in all of the studies. Thus, a careful reviewer should interpret these results with caution.

So why did I decide to highlight this study? In the February 2018 issue of *OB/GYN Clinical Alert,* I reported on the results of a prospective study published by Mørch et al that used Danish databases to evaluate breast cancer risk associated with the use of hormonal contraception.[2] These authors reported results based on 11,517 cases of invasive breast cancer that occurred over 19.6 million woman-years of follow-up during the interval of study. Compared to never users of hormonal contraception, current and recent users of hormonal contraception showed a small increase in risk (relative risk [RR], 1.20; 95% CI, 1.14-1.26). This risk was not increased with less than one year of use (RR, 1.09; 95% CI, 0.96-1.23), but became significant after one year, peaking at 1.38 (95% CI, 1.26-1.51) after 10 years of use. Overall, the increased risk stopped rapidly after discontinuation of a hormonal method, although one analysis suggested that women using hormonal contraception for five to 10 years maintained a small increased risk up to 10 years following discontinuation (RR, 1.3; 95% CI, 1.06-1.58). Similar to the study of Nichols et al, I noted that the Mørch et al study provided some interesting results, but with weak associations that should be interpreted with extreme caution.[3]

The two studies demonstrate a consistent relationship. Mørch et al reported a small increased risk of breast cancer confined to current/recent but not past users of hormonal contraception. This supports the hypothesis that hormonal therapy may promote the growth of pre-existing breast cancers leading to early detection. This result was first described in the Collaborative Reanalysis study from 1996.[4] The rapid disappearance of excess risk after discontinuation of use among women who used hormonal contraception for short periods is what you would expect to see if early detection is occurring with short-term use. Nichols et al provided evidence that pregnancy increases the risk of breast cancer and that the risk remains elevated for many years.

In my opinion, a notable weakness of studies evaluating breast cancer risk associated with hormonal contraceptive use has been the exclusion of pregnant women from the reference group. It now appears that both hormonal contraception and pregnancy likely accelerate the growth of prevalent breast cancers leading to earlier diagnosis. Presenting information on breast cancer risk associated with pregnancy may

help frame the discussion of cancer risk associated with hormonal contraception. Fortunately, the overall excess risk remains very low. ■

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CME/CE INSTRUCTIONS

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CME/CE QUESTIONS

1. Advanced paternal age is known to be associated with which of the following neonatal outcomes?
a. Multiple myeloma
b. Asthma
c. Autism
d. Congenital heart disease

2. Advanced paternal age is associated with which of the following neonatal outcomes?
a. Large for gestational age
b. Hyperbilirubinemia
c. Failure to thrive
d. Preterm birth

3. In the study by Subtil et al, clindamycin was superior to placebo for the prevention of preterm birth in pregnant women with bacterial vaginosis.
a. True
b. False

4. Which of the following statements is correct when describing the results of the study of aspirin and preterm birth?
a. There was a decrease in spontaneous preterm birth at < 34 weeks.
b. There was a decrease in spontaneous preterm birth at < 37 weeks.
c. There was a greater risk of postpartum hemorrhage.
d. There was a decrease in the incidence of placental abruption.

5. The apparent prevention of spontaneous preterm birth associated with aspirin was greater if the drug was administered prior to 16 weeks.
a. True
b. False

6. In the reanalysis of individual data from 15 prospective cohort studies, compared to nulliparous women, the overall risk of breast cancer in parous women was:
a. increased for five years after birth followed by a strong protective effect.
b. decreased only in breastfeeding women.
c. elevated only in breastfeeding women.
d. weakly increased for about 20 years, followed by a weak protective effect.

[IN FUTURE ISSUES]

Brexanolone for Postpartum Depression: Promising, but Will It Deliver?