An ounce of prevention: The evidence supporting periconception health care

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Practice recommendations

- Offer smoking cessation interventions to all women of childbearing age who smoke. (**A**)
- Offer folic acid supplementation to all pregnant women as well as women of childbearing age. (**A**)
- Offer women with diabetes intensive glycemic control before pregnancy. (**B**)
- Offer women who take antiepileptic medications folic acid supplementation and a transition to monotherapy, while avoiding phenytoin and valproic acid if possible. (**B**)
- Screen pregnant women and women of childbearing age to further reduce the incidence of congenital rubella syndrome. (**C**)
- Alcohol cessation advice has not consistently been shown to decrease alcohol intake or morbidity in women. Written information on the fetal effects of alcohol should be provided to women who use alcohol during pregnancy. (**B**)

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This article reviews 6 important, evidence-based recommendations for periconception care: smoking cessation, folic acid supplementation and multivitamin use, diabetes care, epilepsy drug use, rubella immunization, and alcohol abuse. With time so limited during primary care visits, physicians often miss opportunities to provide periconception health care. However, some of the recommendations do not take long to convey. And though others may require significant effort on the part of the physician and patient, the benefits can be substantial.

In 2000, women aged 18 to 44 years made 4.1 million outpatient visits to family physicians.[1] Each of these visits was an opportunity to educate a patient about periconception health. Opportune encounters include well-woman exams, discussions about a negative pregnancy test, and follow-up visits for spontaneous or therapeutic abortions. Sexually active women using less-than-effective birth control (or none at all) would also benefit from preconception counseling. For women of childbearing age who have diabetes or epilepsy, make preconception interventions part of their routine medical care.

SMOKING CESSATION

Twenty-five percent of women of reproductive age in the US are cigarette smokers—higher than the percentage of smokers among all women.[2] Up to

90% continue to smoke during pregnancy.[3] The 2001 Surgeon General's Report on Women and Smoking reports that cigarette smoking causes the highest proportion of preventable problems related to pregnancy and the neonatal period. The report estimates that smoking cessation would reduce all infant deaths by 10%.

How smoking adversely affects pregnancy

One meta-analysis found that women who smoke during pregnancy have significantly increased risks of placenta previa, placental abruption, ectopic pregnancy, and preterm premature rupture of membranes (level of evidence [LOE]: **2a**).[4] Maternal cigarette smoking also increases the risk of stillbirth, intrauterine growth retardation, and sudden infant death syndrome (SIDS). Smoking cessation during pregnancy, especially early on, reduced the risk of most of these conditions.[5]

Interventions that work

The best evidence for the effectiveness of smoking cessation interventions is found in studies of nonpregnant patients. Such evidence would likely be applicable to women seeking preconception care.

Multiple Cochrane Database reviews have addressed smoking cessation in nonpregnant patients. The reviews are meta-analyses of randomized, controlled trials (LOE: **1a**) and provide strong evidence for the value of smoking cessation interventions in the general population. Interventions that increase quit rates include the following: brief physician advice,[6] telephone counseling,[7] nicotine replacement therapy (primarily gum and patches were studied),[8] group therapy,[9] and bupropion or nortriptyline[10] (**Table**).

A Cochrane Database review of smoking cessation in pregnancy found that 6.4% fewer women smoked during the third trimester of pregnancy after intervention (LOE: **1a**).[11] Studies that looked at neonatal outcomes showed a reduction in low birth weight and preterm birth (number needed to treat [NNT]=75 for low birthweight; NNT=90 for preterm birth). There were no differences in other outcomes; however, the trials were not powered to detect such differences. Interventions found to be effective included informing women about the effects of smoking on a fetus and the benefits of quitting, recommending to smokers that they quit, and teaching cognitive-behavioral strategies for smoking cessation.

Data sources

Our data were found through a search of the following databases: Medline, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials, and the American College of Physicians Journal Club. We selected the areas with the strongest evidence available for reduction of congenital anomalies available for review. We also focused on subjects whose interventions proved to be effective in improving neonatal outcomes.

Applying the evidence

Because of the proven reduction in neonatal morbidity, smoking cessation counseling may be the most effective part of periconception care. Advise smoking cessation to all women who smoke, before and during pregnancy (strength of recommendation [SOR]: **A**).

FOLIC ACID AND MULTIVITAMINS

Neural tube defects occur in 1 in 1000 babies delivered in the US. The Medical Research Council Vitamin Study found that mothers who had a child with neural tube defects reduced the risk of having another child with neural tube defects by 72% if they took 4 mg of folic acid a day prior to conception and during the first trimester.[12]

A large primary prevention trial in Hungary showed the risk of anomalies (including neural tube defects) in babies decreased by 46% among mothers randomized to receive folic

TABLE

Effective smoking cessation interventions

Intervention	Number of studies	Number of participants	OR* (95% CI)	NNT
Brief physician advice	16	13,575	1.69 (1.45–1.98)	58
Telephone counseling	13	16,462	1.56 (1.38–1.77)	40
Nicotine replacement therapy	97	37,760	1.74 (1.64–1.86)	16
Group therapy vs self-help	16	4395	1.97 (1.57–2.48)	22
Group therapy vs no treatment	6	775	2.19 (1.42–3.37)	10
Bupropion	16	5374	1.97 (1.67–2.34)	11
Nortriptyline	5	861	2.80 (1.81–4.32)	9
Smoking cessation interventions in pregnancy	34	9945	1.89 (1.67–2.13)	16

*Odds ratio for successful smoking cessation. For an explanation of odds ratios, see the Language of Evidence, page 108.
OR, odds ratio; CI, confidence interval; NNT, number needed to treat

acid.[13] A Cochrane meta-analysis demonstrated a 3-fold decreased risk of a first neural tube defect if women took folic acid. The absolute risk of neural tube defects decreased from 10.2/1000 in the control group to 2.4/1000 in the folic acid group. The NNT to prevent 1 neural tube defect was 847.[14]

Studies have shown that periconception multivitamin intake confers other benefits as well: decreased risk of genitourinary malformations, cleft lip and cleft palate, and neuroectodermal tumors in offspring. In all studies, the multivitamins contained folic acid, but most studies were unable to look at folic acid independently.[15–18]

Optimal dose of folic acid

Studies have attempted to determine the most beneficial dose of folic acid and how it should be consumed (ie, diet, supplementation, fortification). Study results, however, are conflicting.[19,20] In 1992, the US Preventive Services Task Force (USPSTF) recommended women of childbearing age consume 0.4 mg/d folic acid,[21] but it did not make a recommendation on the form of folic acid.

Patient education that works

Women in the US are not fully aware of the benefits of taking multivitamins with folic acid prior to conception and during pregnancy. A 2002 survey showed that only 20% of women knew that folic acid could prevent certain birth defects. Even fewer women knew they have to take folic acid prior to conception (7% in the survey).[22]

Though many studies have shown that education increases awareness about folic acid, only a few have investigated if awareness leads to changes in behavior.[23] In highly motivated women, education does appear to influence behavior changes. A study in Texas showed that women who had children with neural tube defects and had received advice about taking folic acid

prior to subsequent pregnancies were more likely to use supplements than women who did not receive this advice.[24] Another study looked at women planning a pregnancy who had preconception counseling. Counseling about folic acid increased folic acid intake.[25]

The USPSTF expected a 70% decrease in incidence of neural tube defects if its 1992 recommendation was followed. In 1998, the Food and Drug Administration began requiring the fortification of cereal grains at the level of 140 µg/100 g grain. This was expected to increase the intake of folate in women by 100 µg/d and decrease the incidence of neural tube defects by 20%.[26]

Data from the Centers for Disease Control and Prevention (CDC) has shown that folate status had improved significantly in women of childbearing age,[27] and the incidence of neuroblastoma has decreased by 19%, from 37.8/100,000 prior to supplementation to 30.5/100,000 since fortification became mandatory.[28]

Applying the evidence

Increased folic acid intake significantly decreases neural tube defects. Education about folic acid increases vitamin use in motivated women (SOR: **A**). Folic acid supplementation of food is an effective population-based intervention to reduce neural tube defects (SOR: **B**). Folic acid intake by women decreases genitourinary and cleft-lip malformations and neuroblastoma in their infants (SOR: **B**).

DIABETES MELLITUS

Estimates of pregestational diabetes in women of childbearing age range from 1.9% to 3.5%.[29,30] Diabetes has been associated with decreased fertility, spontaneous abortions, and congenital anomalies. Several studies have correlated spontaneous abortion rates with hemoglobin A_{1c} values at the time of conception (LOE: **2a**).[31]

Glycemic control reduces spontaneous abortions

One prospective trial[32] compared the spontaneous abortion rate in diabetic women who receive intensive preconception insulin therapy with the rate in women who receive usual care (LOE: **2b**). A spontaneous abortion rate of 8.4% occurred in the preconception treatment group compared with 28% in the pregnancy care–only group (NNT=5). Limitations of this study include the small number of participants and the lack of randomization. However, given all the benefits of improved glycemic control, preconception glycemic control is recommended to reduce the spontaneous abortion rate in diabetic women (SOR: **B**).

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Other benefits of glycemic control

Major congenital malformations occur in 4% to 11% of infants of diabetic mothers compared with a background rate of 1.2% to 2.1%. Higher values of hemoglobin A_{1c} in the first trimester have been associated with these increased rates of congenital anomalies. However, it is not clear if the association is linear or if a threshold level of hemoglobin A_{1c} exists, above which the anomaly rate increases. Anomalies most commonly occur in the cardiovascular, skeletal, and central nervous systems before 8 weeks gestational age. Therefore, the critical time for preventing congenital anomalies is before conception.

Preconception care reduces anomalies overall

One meta-analysis of 16 studies provides evidence for the value of preconception care in reducing congenital anomalies due to diabetes mellitus.[33] The interventions included both inpatient and outpatient optimization of glucose control. The analysis reviews 8 prospective and 8 retrospective cohort studies with a total of 2651 offspring. The results of all 16 studies were consistent.

Hemoglobin A_{1c} values were significantly lower in the preconception care group. The overall rate for major congenital anomalies was 2.1% in the

Preconception glycemic control helps prevent congenital anomalies in children of women with diabetes

preconception group compared with 6.5% in the pregnancy care group (NNT=23) (LOE: **2a**). The studies with the lowest anomaly rates had a premeal glucose target of <120 mg/dL, and participants injected insulin 4 times daily. A cost-benefit analysis based on a mathematical model of preconception diabetic care calculated that intensive preconception care for women with diabetes would save an average of $1720 per enrollee when adverse maternal and neonatal outcomes are taken into account.[34]

Intensive preconception glycemic control helps prevent major congenital anomalies in children born to women with diabetes (SOR: **B**).

EPILEPSY

Compared with healthy women, women with epilepsy have higher rates of infertility and miscarriage and higher rates of infants with congenital anomalies (4%–8%; mainly neural tube defects and heart defects).[35] Therefore, women with epilepsy (5.6/1000 among women aged 15 to 64[36]) should receive special attention to preconception care. Adding to the urgency for counseling is the fact that medications for epilepsy can reduce the effectiveness of some forms of hormonal contraception.

Medications are the problem

A source of debate has been whether the increased rate of anomalies is due to epilepsy or the medications used to treat it. A cohort study compared 3 groups of pregnant women: those taking antiepileptic medications (some were taking these medications for other conditions, such as bipolar disorder), women with epilepsy who were not on medications, and a control group. The rate of major and minor malformations among infants of women taking antiepileptic medications was 20.6%, compared with 8.5% in the control group (LOE: **2b**).[37] Women with epilepsy who were not on medications had a similar anomaly rate to the control group.

The medications primarily associated with congenital anomalies were valproic acid, carbamazepine, and phenytoin; polytherapy was associated with a higher anomaly rate. The data on newer antiepileptic medications (eg, gabapentin, lamotrigine, oxcarbazepine, tiagabine, topiramate, and vigabatrin) are insufficient to determine if anomaly rates are increased among fetuses exposed to them.[38] Because folic acid supplementation has been associated with lower rates of infants with neural tube defects, higher-dose folic acid supplementation (1–4 mg/d) has been recommended for women with epilepsy (LOE: **5**).

Change treatment before conception

One cohort study has examined the effectiveness of preconception counseling for women with epilepsy.[39] The investigators compared women referred to a preconception epilepsy clinic with women who presented during pregnancy. In the preconception group, all women were placed on folic acid, two thirds were shifted to monotherapy prior to conception, and 6% were able to stop their epilepsy medications. The epilepsy clinic followed a protocol for confirming the diagnosis of epilepsy, determining if a woman was a candidate to discontinue medications, avoiding use of phenytoin and valproic acid, and switching as many women to monotherapy as possible.

The preconception care group had no major fetal malformations, compared with 18% in the pregnancy group (NNT=6) (LOE: **2b**).

Applying the evidence

On the basis of this study, women with epilepsy who are considering pregnancy should be switched to monotherapy and potentially less teratogenic medications (when possible), and should receive at least 1 mg/d folic acid prior to conception (SOR: **B**).

RUBELLA

Immunization has reduced the occurrence of rubella in the US from 57,686 cases in 1969 (when vaccination was started) to 279 cases in 1999.[40] Cases of congenital rubella syndrome in the US have fallen to a low of 3 cases in 2001. However, rubella and congenital rubella syndrome are still fairly common in developing countries, many of which have no rubella vaccine program or have only recently started such programs.

In the US, rubella infection is most likely to occur among Hispanic patients (especially foreign-born patients) and among families that refuse immunization.[41] A review of 12 cases of congenital rubella after an outbreak in the early 1990s found that more than 50% of the mothers had 2 or more medical visits where rubella testing/immunization could have been done. Similarly, another study found that 62% of women who gave birth to infants with congenital rubella syndrome had at least 1 missed opportunity for immunization prior to that pregnancy.[42]

Although no prospective studies confirm this observation, the authors calculated that the single most effective policy for prevention of congenital rubella syndrome would be screening pregnant women for rubella immunity and postpartum immunization of nonimmune women (SOR: **C**).

ALCOHOL

The Institute of Medicine recognizes alcohol-related birth defects (ARBD) and alcohol-related neurodevelopmental disorder (ARND) in addition to fetal alcohol syndrome (FAS) as potential effects of alcohol use in pregnancy and the periconception period.[43]

A diagnosis of FAS requires characteristic facial anomalies, growth retardation, and neurodevelopmental abnormalities. A category of partial FAS does exist; affected children have some of the characteristic facial anomalies, and either growth retardation, neurodevelopmental abnormalities, or cognitive/behavioral abnormalities with no other explanation.

ARBD includes a confirmed history of maternal alcohol use plus one or more congenital defects (most commonly cardiac, renal, vision, hearing, or skeletal. ARND requires a confirmed history of maternal alcohol use and either the neurodevelopmental abnormalities or cognitive/behavioral abnormalities found in partial FAS.

The prevalence of FAS in the US population is estimated at 0.5 to 2 per 1000 births, with up to 10/1000 newborns having some effect from alcohol exposure.[44] The rate of FAS is more than 20 times higher in the US compared with other countries, including European countries, partially due to differences in diagnosis.[45]

Strict abstinence required?

Whether a safe threshold of alcohol consumption exists before or during pregnancy is a point of controversy. Many US authorities recommend against any alcohol intake before or during pregnancy. The effects of alcohol on a fetus depend on the amount of alcohol consumed at one time, timing of alcohol consumption in gestation, and duration of alcohol use in pregnancy.

This is complicated by the fact that studies have used varying definitions of light and heavy alcohol use, with categories that often overlap between different studies.[46] Binge drinking (defined as more than 5 drinks on a single day), even when episodic, is more dangerous to fetal brain development than nonbinge drinking.[47]

Less severe problems can occur

Although a high level of alcohol use in pregnancy is associated with more severely affected offspring, a 1984 study of 31,000 pregnancies showed a higher risk of growth retardation if a mother had even 1 drink a day (LOE: **2b**).[48] A 2001 study of more than 600 urban African American children showed continued behavioral effects of alcohol at ages 6 to 7 with low levels (1 drink daily) of maternal alcohol consumption (LOE: **2b**).[49]

Some intervention attempts show promise

A review of trials in which physicians briefly counseled nonpregnant women who were problem drinkers found no consistent decrease in drinking.[50] Trials of personalized advice to pregnant women have also found it to be no more effective than written information alone.[51] A written self-help manual, however, did improve cessation rates among women at a prenatal clinic.[52]

The CDC sponsored a pilot project to encourage alcohol cessation and effective contraception in women at risk for alcohol-exposed pregnancy.[53] Although not a controlled trial, this more extensive intervention showed promise. Of the 143 women enrolled, 68.5% had either stopped their alcohol consumption or were using effective contraception by the 6-month follow up.

Applying the evidence

Written information about the risks of alcohol use in pregnancy should be provided to pregnant women who consume alcohol (SOR: **B**). There is not enough data to recommend physician counseling for alcohol cessation before or during pregnancy. More comprehensive interventions may be more effective, but have yet to be fully studied. No studies have evaluated neonatal outcomes in the offspring of women who are counseled on alcohol cessation in the periconception period.

DRUG BRAND NAMES

Bupropion • Zyban
Carbamazepine • Atretol, Depitol, Epitol, Tegretol
Gabapentin • Neurontin
Lamotrigine • Lamictal
Nortriptyline • Aventyl, Pamelor
Oxcarbazepine • Trileptal
Phenytoin • Cerebyx, Dilantin, Mesantoin, Peganone, Phenytek
Tiagabine • Gabitril
Topiramate • Topamax
Valproic acid • Depakene, Depakote
Vigabatrin • Sabril (available only in Canada)

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