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NEWBORN LENGTH OF STAY

References Brumfield CG, Nelson KG, Stotser D, et al. 24-hour mother-infant discharge with a follow-up home health visit: results in a selected Medicaid population. Obstet Gynecol 1996; 88:544-8. Beebe SA, Britton JR, Britton HL, Fan P, Jepson B. Neonatal mortality and length of newborn hospital stay. Pediatrics 1996; 98:321-35.

Clinical question **Are infants discharged within 24 hours after birth at greater risk of death or hospital readmission?**

Background In the "good old days," women and their newborns would stay in the hospital for several days after delivery. Women were happy, hospitals were happy, doctors were happy, and we drove up the cost of care. Over the past two decades, the length of stay has gradually declined. This decline is due to changes in medical practice, changes in reimbursement, and patient preferences. Currently, managed care organizations have implemented 24-hour discharge policies that have come under fire from many quarters. Two recent studies evaluate outcomes of infants discharged 24 hours after birth.

Population studied Brumfield and coworkers report a case series of low-risk pregnancies in Medicaid patients at the University of Alabama at Birmingham. Women were eligible for 24-hour discharge if they had no medical problems, no history of substance abuse, had an uncomplicated delivery (defined by the degree of perineal trauma) and postpartum course, and if at least 12 hours had elapsed since postpartum tubal ligation. Infants were eligible if they were at term, weighed at least 2500 g, and had a normal examination 24 hours later. Every effort was made to send mother and baby home as a unit. A visiting nurse visited each mother and infant 48 hours after delivery.

Beebe and colleagues performed a case-control study in Utah. They reviewed death certificates for all infants with birthweight over 2500 g born at term. The authors identified 109,256 eligible births and found 115 deaths in the first 28 days of life. Of these deaths, 84 neonates had been transferred to another hospital after birth, 5 were hospitalized for more than 5 days, and 9 records could not be located. The authors found 17 deaths of infants who were presumably healthy and were discharged from the hospital at 5 days of age or younger. The authors matched three controls for each case on the following variables: hospital, sex, county of residence, marital status, parity, mother's education level, race, gestational age, month of first prenatal visit, and date of birth.

Study design and validity The case series is among the weakest of methods and one should exercise extreme caution in making judgments based on such studies. Brumfield is unable to report whether the "usual care" group had more or fewer phone consultations, office visits, or hospital admissions. Beebe and colleagues report that for their case-control study to have 80% power to detect a 2:1 odds ratio, they would need to observe 96 deaths. Using their data, one would still need to study 800,000 births to achieve this! They only had 22% power to detect an odds ratio of 2.0 or greater. When studying rare events, case-control studies are reasonable as long as one acknowledges the weaknesses inherent in such a design. Beebe and colleagues supplemented the death records with an audit of the hospital records. Ideally, this issue would be studied in a randomized prospective study. However, if the death rates for low-risk and high-risk infants are 3 and 6 per 10,000 births, respectively, one would need just under 8 million patients in each group!

Outcomes measured Brumfield reports the rate of telephone consultation with physicians, clinic visits for evaluation of problems, hospital readmissions, and financial savings. Beebe reports the cause of death according to the death certificate and tried to identify "symptomatic" infants.

Results Brumfield identified 972 eligible women (17% of the deliveries) and found that 15 women (1.5%) had problems that required a phone consultation with an obstetrician, 7 were seen in the clinic, and 2 of these 7 were readmitted to the hospital (1 for hypertension, 1 for wound infection). Eight hundred fifty-six newborns (15% of the deliveries) were eligible for the 24-hour dis-

charge program, 795 (93%) of whom had a normal exam at the time of the nurse visit. The nurse identified problems requiring a phone call to a pediatrician in 61 infants. Twelve were seen by the pediatrician, and none were admitted to the hospital. The most common problems the nurse identified were jaundice (n=24), infant care (n=20), and heart murmur (n=9). The net savings to the hospital was $506,139 during a 2-year period.

Beebe et al found no difference in mean age at discharge between the 17 infants who died and the healthy controls (43 ± 21 hours vs 47 ± 25 hours). They also found no association between neonatal mortality and the following variables: sex, race, marital status, education, maternal age younger than 20, and birthweight less than 3000 g. Maternal age over 30 was significantly associated with increased neonatal mortality (OR = 5.45, P = .0435). Hospital length of stay less than 24 hours was not significantly associated with neonatal mortality (OR = 1.65, 95% CI, 0.42 to 6.43). Similarly, hospital stay less than 48 hours also was not significantly associated with neonatal mortality (OR = 1.16, 95% CI, 0.40 to 3.34). Of the 84 infants who were transferred to other hospitals, 93% had been symptomatic by 12 hours of age and 99% were symptomatic by 18 hours of age.

Recommendations for clinical practice **Brumfield confirms that even with the added cost of paying nurses to make home visits, hospitals may save money when low-risk women and infants are discharged at 24 hours. Beebe et al show a nonsignificant trend toward increased risk of neonatal mortality, but it lacks sufficient power. While they believe that infants at risk were identifiable early in their stay, this is based on the observation that tests such as blood gases or radiographs were ordered. They do not report which "symptoms" identified these high-risk infants. While the trend in Beebe's study suggests infants are at greater risk of death if discharged early, the study does not have adequate power to definitively answer this question.**

This issue is emotion laden and has introduced at least two parties into the usual decision-making process between patients and physicians: insurance companies and government. Recently the President signed legislation requiring insurance companies to pay for 48 hours in the hospital after delivery. It may or may not, in fact, be safe to send mothers and babies home less than 24 hours after delivery. That choice and the ability to systematically evaluate its outcomes may be moot.

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Topical Ointments and Wound Healing

Reference Smack DP, Harrington AC, Dunn C, et al. Infection and allergy incidence in ambulatory surgery patients using white petrolatum vs bacitracin ointment: a randomized controlled trial. JAMA 1996; 276:972-7.

Clinical question **Is there a difference between the effect of white petrolatum and bacitracin ointment on wound infection and allergy incidence?**

Background Topical ointments help healing by keeping skin wounds moist, promoting epithelialization and serving as an occlusive barrier. Data support the use of antibiotic-containing ointments in place of plain ointments when treating contaminated wounds. Support for the use of antibiotic-containing ointments in the postprocedure care of clean wounds is lacking. Antibiotic ointments are more expensive than inert agents and can risk the development of resistant bacteria and allergic contact dermatitis (ACD).

Population studied All consenting eligible patients undergoing a surgical procedure in the dermatology clinic at Walter Reed Hospital, Washington, DC, were included. Exclusion criteria included pregnancy, age less than 18 years, bacitracin ointment allergy, infection prior to the procedure, known HIV positivity, or requirement of pre-procedure antibiotic prophylaxis.

Study design and validity Study subjects were randomly assigned in a double-blind fashion to receive a container of either bacitracin ointment or white petrolatum. Each wound site was prepared with chlorhexidene scrub and subsequently cleansed with a peroxide solution after the procedure, at home and during follow-up visits. It is not standard practice to use peroxide at each wound dressing, and the incidence of infection may thus be higher for wounds not cared for similarly. Patients applied the study ointment after each cleaning. Follow-up continued for a total of 4 weeks. Wound cultures were obtained and systemic antibiotics were initiated for any wounds appearing to be infected. Highly "itchy" wounds were patch-tested with bacitracin, neomycin, and white petrolatum for confirmation of ACD. Both physician blinding and patient compliance were assessed and deemed adequate.

Outcomes measured Wound sites were subjectively assessed for the presence and degree of erythema, tenderness, and purulent drainage. Extensive pruritis and a positive patch test defined an ACD reaction. Clinical healing was described as wound open/closed, scab/eschar, or mature scar.

Results Of the 922 patients initially enrolled in the study, 38 were lost to follow-up. The two treatment

groups were similar at baseline regarding number and location of wounds, type of procedure performed, age, and sex. Thirteen patients developed postprocedure infection (1.5%), 9 (2.0%) in the white petrolatum group vs 4 (0.9%) in the bacitracin group (95% CI for difference, -0.4% to 2.7%; P = .37). Eight infections in the white petrolatum group were due to *Staphylococcus aureus* vs none in the bacitracin group. Cultures from the bacitracin group grew predominately gram-negative bacteria. No patient in the group using white petrolatum developed ACD vs 4 patients (0.9%) in the bacitracin group. There were no clinically significant differences in healing rates between the two groups.

Recommendations for clinical practice **White petrolatum is a safe, effective wound care ointment for ambulatory surgery. In comparison with bacitracin ointment, white petrolatum possesses an equally low infection rate and minimal risk for induction of allergy. Wounds treated with bacitracin may result in allergic reactions or gram-negative bacterial infections requiring expensive treatments. The authors of this study estimate a cost savings of $8 to $10 million annually in the United States if practitioners use white petrolatum instead of topical antibiotics for clean wounds. Note that infection rates with uncomplicated traumatic wounds are increased with the use of white petrolatum compared with bacitracin ointment.**[1]

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Treatment of Hyperlipidemia in Women

Reference Buchwald H, Campos CT, Boen JR, et al. Gender-based mortality follow-up from the program on the surgical control of the hyperlidemias (POSCH) and meta-analysis of lipid intervention trials: women in POSCH and other trials. Ann Surg 1996; 224: 486-500.

Clinical question **Do interventions to reduce serum lipids in women reduce overall mortality?**

Background A number of studies have evaluated the effectiveness of various forms of lipid therapy on overall mortality. Several have failed to show lower mortality, while others such as the Scandanavian Simvastatin Survival Study have demonstrated reduced mortality among those treated.[1] None of these studies, however, has demonstrated a survival advantage for women treated for hyperlipidemia.

Population studied The seven trials included somewhat differing populations. Some were primary prevention trials of patients who had not yet had coronary events, others were secondary prevention trials of patients who had already had coronary artery disease, and some included both groups. Interventions included dietary, pharmacologic, and surgical (partial ileal bypass) treatment of hyperlipidemia. All analyzed the effect of a lipid intervention on overall mortality and included data that allowed calculation of gender-specific mortality rates.

Study design This was a meta-analysis of seven trials that combined the results of several studies to determine a summary treatment effect. Inclusion criteria were broad, with considerable variability among the trials in terms of the intervention. Statistical methods were appropriate, and the authors reported results for both fixed and random effects models. The latter does not assume a uniform effect, and may be a more robust meta-analytic method.

Outcomes measured Overall mortality for all participants and gender-specific overall mortality were the primary outcomes.

Results Of the 11,173 men in the seven trials, 579 (10.3%) in the control group and 463 (8.3%) in the intervention group died. Of the 7066 women in the seven trials, 164 (4.7%) in the control group and 169 (4.8%) in the intervention group died. The pooled risk difference was statistically significant for men (P = .048), but not for women (P = .39). The POSCH trial results alone show no significant overall mortality reduction for men or women. However, men did have significant reductions in ACHD mortality or definite nonfatal myocardial infarction, while the women did not show significant reductions in these outcomes.

Recommendations for clinical practice **Using the techniques of meta-analysis, this study failed to find any statistically significant reduction in overall mortality from lipid treatment. Before accepting these conclusions, readers should decide if the included studies are similar enough to merit combined analysis. Although the authors found no statistically significant differences among the included studies, there may be clinically relevant distinctions. A second concern is the limited power of the included studies to detect a mortality difference in women. The number of deaths among women was only 24% of the total mortality. Moreover, 66% of the intervention deaths and 58%**

of the control deaths occurred in the Minnesota Coronary Study, which used diet therapy alone.[2] Thus, a larger study of women using a pharmacologic intervention might have the potential to show different results than the current meta-analysis.

These concerns call into question the conclusions of the current study. Indeed, the authors themselves caution that physicians should not abandon lipid intervention in women, particularly in those with coronary artery disease. (Editor's note: see this month's Journal Club review on lipid-lowering agents in post-MI patients, which found a greater reduction in coronary events among women than men).

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2. Franz ID Jr, Dawson EA, Ashman PL, et al. Test of the effect of lipid lowering by diet on cardiovascular risk: the Minnesota Coronary Survey. Arteriosclerosis 1989; 9:129-35.

ANTICOAGULANTS IN ACUTE MI

Reference Collins R, MacMahon S, Flather M, et al. Clinical effect of anticoagulant therapy in suspected acute myocardial infarction: systematic overview of randomized trials. BMJ 1996; 313:652-9.

Clinical question **What are the effects of heparin alone, and of adding heparin to aspirin, in the treatment of patients suspected of having an acute myocardial infarction (AMI)?**

Background The Second International Study of Infarct Survival (ISIS-2) established reductions in mortality in AMI of 23% using aspirin alone, 30% using streptokinase alone, and 52% using both. The American College of Cardiology/American Heart Association Task Force recommends the use of heparin in addition to aspirin and fibrinolytic therapy despite the lack of definitive clinical trials.

Population studied Studies for this meta-analysis were retrieved by using computer-aided searches, reviewing reference lists, and contacting other investigators and pharmaceutical companies. However, the precise databases, languages, and years searched were not stated. Studies were included if they were randomized trials of anticoagulant therapy in the acute phase of suspected myocardial infarction. They were excluded if investigators could predict the assignment of patients before recruiting them, if the studies were comparisons between different heparin regimens, or if another confounding intervention was identified. A total of 68,000 patients in six trials were used to assess the effect of adding heparin to aspirin and fibrinolytic therapy.

Study design and validity This is a meta-analysis, a type of review article that uses quantitative methods to summarize the results from clinical trials. It was not explicitly stated whether the individual articles were appraised for quality. Unpublished studies were not included, which could lead to publication bias since unpublished studies are more likely to have shown no treatment effect. However, publication bias is of less concern in a meta-analysis that shows little effect. The studies were homogeneous, so any differences in the size of the effect between the studies is likely due to chance alone rather than systematic differences among the studies. The only exception to this was for the outcome of stroke in the studies done without aspirin. Summary results were reported as odds reductions with their 95% confidence intervals (CI). The "number needed to treat" (NNT) to prevent one death, reinfarction, or pulmonary embolism and the "number needed to harm" (NNH) to cause one excess episode for major bleeding were derived from the reported rates per thousand treated. The mean duration of follow-up for all studies was 10 days.

Outcomes measured The primary outcomes were the rates of death, reinfarction, and stroke in the hospital. While data for pulmonary embolism were reported, the studies analyzed were not designed to detect pulmonary embolism. Data for major bleeding (using varying definitions) was consistently reported for the aspirin studies only.

Results Heparin reduced the death rate by 6% (95% CI, 0% to 10%, NNT = 200) and reinfarction rate by 9% (95% CI, 0% to 20%, NNT = 333). There was no significant effect on stroke rate. The addition of heparin decreased PE by 30% (95% CI estimated from graph 20% to 55%, NNT = 1000). Major bleeding was increased by heparin by 42% (95% CI not given, NNH = 333). For the second question, 5000 patients in 21 trials were analyzed to assess heparin alone or with oral anticoagulant. Anticoagulation reduced the death rate by 25% (95% CI, 10% to 38%, NNT = 29). There was no significant effect on reinfarction. Stroke was reduced 48% (95% CI, 16% to 66%, NNT = 100). Major noncerebral bleeding was consistently reported only for high-dose heparin (>20,000 IU/day), which resulted in a doubling in the absolute risk corresponding to one excess episode for every 77 patients treated.

Recommendations for clinical practice **All patients with AMI should be treated with aspirin. For patients with a history of anaphylaxis to aspirin, heparin should be used. In this meta-analysis heparin added to aspirin leads to a further 6% decrease in mortality, but a firm recommendation for its use cannot be made since the confidence intervals include the possibility that no benefit is obtained and the follow-up interval was only 10 days. Though not unequivocally established by this study, there is also a possibility that heparin will result in more episodes of major bleeding.**

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■ Acylovir in Pregnancy for Primary Prevention of Neonatal Herpes

Reference Randolph AG, Hartshorn RM, Washington AE. Acyclovir prophylaxis in late pregnancy to prevent neonatal herpes: a cost-effectiveness analysis. Obstet Gynecol 1996; 88:603-10.

Clinical question **Is the administration of oral acyclovir to pregnant women with recurrent herpes cost-effective for preventing neonatal herpes?**

Background Up to one third of all pregnant women have been exposed to herpes and may be at risk for transmitting the infection during childbirth. The current standard of care in many hospitals is a cesarean section for active herpes lesions present during labor. Recent evidence suggests that acyclovir late in pregnancy may decrease the frequency of recurrent active lesions. This analysis incorporates this new evidence and reassesses the data supporting the current standard of care.

Population studied The study population consisted of a hypothetical cohort of 10,000 pregnant women at 37 weeks' gestation with at least one previous clinically documented episode of genital herpes.

Study design and validity This well-designed cost-effectiveness analysis looked at four main strategies in the decision tree: (1) no drug treatment but cesarean section if active herpes lesions are present at the time of delivery, (2) acyclovir prophylaxis from 37 weeks and cesarean section if active lesions are present, (3) acyclovir prophylaxis and vaginal delivery even if active herpes lesions are present, and (4) no intervention. The decision tree considered all important outcomes, including long-term costs and sequelae of neurologic damage from neonatal herpes. The evidence for all probabilities in the tree was presented and referenced. The estimates of acyclovir's benefit were based on two randomized controlled trials that evaluated its effect on prevention of active herpes lesions. Extrapolation was then made to an effect on prevention of neonatal herpes. The estimates of the benefits of cesarean section were based only on expert opinion. The authors acknowledge that there are no data to support this opinion. Appropriate sensitivity analyses (varying the probability of each intermediate step through a range of possibilities) were presented. Viral resistance was not considered in the analysis. It would be helpful to know how increasing levels of resistance would affect the analysis.

Outcomes measured Primary outcomes measured were the frequency of infections, morbidity and mortality, the direct cost per neonatal life saved, and the direct cost for prevention of long-term neurologic sequelae associated with each strategy.

Results In this analysis, the use of acyclovir is clearly beneficial. Cesarean section appears beneficial but the true effect is unknown because the data are inadequate. The rate of neonatal infection per 10,000 women followed for each of the four strategies listed above is: (A) no drug/cesarean, 3.4; (B) acyclovir/cesarean, 0.7; (C) acyclovir/no cesarean, 1.2; and (D) no drug/no cesarean, 6.2.

Costs for each case of neonatal herpes prevented (compared with strategy D) are $1,319,457 for strategy A; $493,641 for strategy B; and $400,382 for strategy C. Costs per case of neonatal death or disability prevented are $3,012,459 for strategy A; $1,127,034 for strategy B; and $914,114 for strategy C.

Recommendations for clinical practice **A policy of routine drug prophylaxis for pregnant women with recurrent genital herpes is cost-effective. The evidence for the effectiveness of acylovir is based on trials looking at intermediate outcomes. Thus, the true effectiveness of acylovir on neonatal infection may be greater because (theoretically) acyclovir may decrease the viral load present in active lesions and reduce the transmission rate. Acyclovir is currently not approved for use in pregnant women. Assuming that it is proven safe for use in the third trimester, providers should offer prophylactic acyclovir to pregnant women with a history of genital herpes. The data are too weak to make a strong recommendation for or against prophylactic cesarean section. Until more definitive patient-oriented evidence is available, the decision to use acylovir prophylaxis and/or to**

perform a cesarean section remains a matter of informed consent.

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Lipid Lowering in Post-MI Patients with Normal Cholesterol

Reference Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. N Engl J Med 1996; 335:1001-9.

Clinical question **Will cholesterol lowering therapy decrease death from coronary heart disease (CHD) or nonfatal myocardial infarction (MI) in patients who have had a previous MI and who have average plasma cholesterol concentrations?**

Background Two recent landmark trials have demonstrated the benefits of cholesterol lowering with "statin" therapy for the primary and secondary prevention of fatal and nonfatal CHD in patients with hypercholesterolemia. To further define the role of pharmacologic interventions, the Cholesterol and Recurrent Events (CARE) Trial evaluated the effectiveness of pravastatin in preventing coronary events after myocardial infarction in patients with average cholesterol concentrations.

Population studied Men and postmenopausal women between the ages of 21 and 75 years with a history of MI within the 3 to 20 months prior to randomization were included in the study. Inclusion criteria were: plasma total cholesterol level less than 240 mg/dL, LDL cholesterol between 115 and 174 mg/dL, and triglyceride less than 350 mg/dL. Exclusion criteria were: fasting glucose level greater than 220 mg/dL, left ventricular ejection fraction less than 25%, symptomatic CHF, the absence of coronary atherosclerosis on arteriogram, or the presence of a significant noncardiovascular disease.

Study design and validity After a pre-randomization screening period, patients randomly received either pravastatin 40 mg daily or placebo. Both groups participated in a structured dietary program throughout the trial. The average duration of follow-up was 5 years. With the exception of an increased use of oral hypoglycemic agents in the placebo group, there were no other significant differences in demographic characteristics between the groups. All analyses were performed on an intention-to-treat basis.

Outcomes measured The combined endpoint of fatal CHD or a nonfatal MI was the primary outcome of the study. The incidence of coronary events was also stratified by differences in baseline variables. Other outcomes measured included the rate of coronary artery bypass grafting (CABG) and angioplasty, stroke, adverse events, mortality from noncardiovascular causes, and overall mortality.

Results The combined incidence of fatal CHD or nonfatal MI was significantly lower with pravastatin than with placebo (10.2% vs 13.2%, P=.003). Independently, the rate of nonfatal MI was significantly reduced, whereas death from CHD was not. The decrease in the rate of the primary endpoint was not altered by the patient's age at baseline, the presence of hypertension or diabetes, smoking status, or left ventricular ejection fraction. When stratified for LDL levels, the reduction in the rate of coronary events with pravastatin was greater in patients with higher baseline LDL levels. No benefit from treatment was observed in patients with LDL levels of 125 mg/dL or less. The effect of pravastatin on coronary events was greater among women than among men (46% lower for women and 20% lower for men). The risk of CABG and angioplasty was reduced 27% and the risk of stroke was reduced 31% in the pravastatin group. More patients in the placebo group discontinued their medication than in the active treatment group (P=.007). There were no significant differences in mortality from noncardiovascular causes and overall mortality between the groups.

Recommendations for clinical practice **This study reaffirms that cholesterol lowering therapy prevents cardiovascular events provided LDL concentrations are greater than 125 mg/dL. Based on these data, clinicians would need to treat 55 patients with pravastatin for 5 years to prevent one nonfatal MI. To prevent a single primary outcome (combined death from CHD or nonfatal MI), clinicians would need to treat 33 patients. Drug costs for this 5-year period would total approximately $6,300 per person. Consistent with other studies, the treatment effect of pravastatin begins after approximately 2 years. Clinicians should temper their decision to treat patients with average cholesterol concentrations and a previous MI with the realization that overall mortality is not likely to be impacted by pravastatin therapy. Quality-of-life issues and cost-effectiveness analyses should clarify this issue, however.**

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Intravaginal Misoprostol: A New Option for Labor Induction?

Reference Mundle WR, Young DC. Vaginal misoprostol for induction of labor: a randomized controlled trial. Obstet Gynecol 1996; 88:521-5.

Clinical question **Is the vaginal application of misoprostol a safe and effective method for induction of labor at term?**

Background Common methods for labor induction include intracervical or intravaginal prostaglandins, oxytocin infusion, or some combination thereof. These preparations are significantly more costly than misoprostol, a synthetic prostaglandin E_1 analog. Previous studies, although small, have shown misoprostol to be successful in inducing labor without ill effects to the mother or neonate.

Population studied Women with term singleton pregnancies, intact membranes, cephalic presentation, and an indication for induction were eligible. Patients were excluded if they had a history of uterine surgery, known hypersensitivity to prostaglandins, any contraindication to vaginal birth, or if they developed nonreassuring fetal heart rate tracings.

Study design and validity Consenting women were randomized to receive either one half of a 100-µg misoprostol tablet intravaginally every 4 hours until labor, delivery, or nonreassuring fetal heart tones; or standard care, which consisted of a physician-chosen combination of prostaglandin gel every 6 hours and oxytocin. Once membranes were ruptured, any further induction was done by oxytocin alone. Neither patients nor caregivers were blinded to group assignment; the neonatal team was, however, unaware of group assignment.

Outcomes measured The primary outcome measured was the time from onset of induction to vaginal delivery. Additionally, maternal outcomes (perineal trauma, delivery interventions, intrapartum events), neonatal outcomes (cord pH, Apgar scores, morbidity), and costs were compared between the two groups.

Results Each arm of the study included 111 women; follow-up was 100% complete. The two groups were comparable in gravidity, parity, gestational age, maternal age, Bishop scores, and indications for induction. No mention was made of the percentage of eligible women who consented to be randomized, nor of the comparability of those who did and did not consent.

Although there was no difference in the rate of cesarean deliveries (10.8% standard induction vs 13.5% misoprostol), the control group had a statistically significant increase in the number of assisted vaginal deliveries. Women in the misoprostol arm were statistically less likely to have received oxytocin or an epidural (RR, 0.48 and 0.62, respectively). No difference was found in the rates of meconium staining, development of nonreassuring fetal heart tones, episiotomy, or perineal lacerations. No infant in either group had significant morbidity (respiratory distress, meconium aspiration, seizures, or neurologic abnormalities), nor were there any significant differences in Apgar scores or cord pH values.

Excluding those who underwent cesarean section, mean time from onset of induction to delivery was 753 minutes for those randomized to misoprostol as compared with 941 minutes for those receiving standard care (P=.018). The lack of clinician blinding may have influenced the aggressiveness of oxytocin therapy differentially between the two groups. It is unlikely, however, that such a bias would overturn the results to favor traditional prostaglandins.

Cost analysis was limited to the expense of the prostaglandin product alone. Median values were $0.22 and $70.00 for the misoprostol and the standard induction group, respectively.

Recommendations for clinical practice **In this study, misoprostol reduced time from labor onset to vaginal delivery by more than 3 hours as compared with a standard protocol. Misoprostol appears safe for both the mother and baby. Rare long-term sequelae will be discovered only through increased experience with the intravaginal use of this drug. Although this study did not describe misoprostol's side-effect profile, pooling dropout rates is the preferred method to compare drug tolerability. Follow-up was complete in this study and there was no mention of patients' inability to tolerate continued dosing of either treatment regimen. Although net costs were not calculated, the lower cost of misoprostol, combined with the decreased use of oxytocin, epidurals, surgical interventions at delivery, and the possible shortened hospital stays, suggests an overall cost savings by using misoprostol. With mounting evidence demonstrating its safety and efficacy, misoprostol should be considered an option for labor induction.**

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Birth Outcomes in Pregnant Women Taking Fluoxetine

Reference Chambers CD, Johnson KA, Dick LM, Felix RJ, Jones KL. Birth outcomes in pregnant women taking fluoxetine. N Engl J Med 1996; 335:1010-5.

Clinical question **Is fluoxetine (Prozac) safe to use in pregnant women?**

Background Fluoxetine (Prozac), a selective serotonin reuptake inhibitor, has become the most frequently prescribed antidepressant agent in the United States. Although the FDA categorizes flouxetine as Pregnancy Category B, its use during pregnancy has not been thoroughly evaluated.[1] This study was designed to determine the treatment effects of fluoxetine during the first trimester on the incidence of structural anomalies and the treatment effects during the third trimester on perinatal complications and neonatal adaptation.

Population studied The population consisted of 228 pregnant women exposed to fluoxetine and 254 controls. The 228 cohort patients were further divided into an exposed early (discontinued fluoxetine before 25 weeks' gestation) or an exposed late (continued to take fluoxetine after 24 weeks' gestation) group. Depression was the most common indication for fluoxetine; the average fluoxetine dose was 28±15 mg in the exposed-early group and 25±10 mg in the exposed-late group. Approximately 30% of women in both fluoxetine groups were taking other psychotropic drugs, with benzodiazepines being the most common. Early prenatal care was instituted in the majority of all enrollees. Concurrent alcohol or recreational drug use was infrequently reported; however, more women smoked in the fluoxetine groups. The control group was significantly younger (30±5 years vs 32±5 to 6 years), although this difference is probably not clinically significant.

Study design and validity In this nonrandomized prospective trial, the authors identified patients for fluoxetine exposure or a nonteratogenic exposure through calls placed to the California Teratogen Information Service and Clinical Research Program. The time of the telephone call was the only matching criterion between the fluoxetine-treated and nontreated women, thus not controlling for the effects of depression and other psychiatric disorders on birth outcomes. All enrollees completed a questionnaire that included past medical and obstetrical history, demographic information, and exposure history. In addition, all women kept a diary and were called by the investigators to record any additional exposures throughout pregnancy. Birth outcome was recorded by the mother's report, medical record review, primary physician evaluation, and examination by one of the investigators, when possible.

Outcomes measured The primary outcomes measured were the frequency of major and minor structural anomalies with fluoxetine exposure during the first trimester and the incidence of perinatal complications with exposure during the third trimester. Major and minor structural anomalies were defined as occurring in < 4% of the general population and having or not having cosmetic or functional importance, respectively.

Results The incidence of major structural anomalies was not significantly different between the fluoxetine groups and the control group (5.5% vs 4.0%). The rate of spontaneous pregnancy loss also did not differ between the fluoxetine-exposed groups and the control group (10.5% vs 9.1%). The incidence of three or more minor structural anomalies was significantly higher in the fluoxetine-exposed infants (15.5% vs 6.5%). The authors did not characterize the types of minor anomalies observed. Infants exposed to fluoxetine in the third trimester had significantly higher rates of premature delivery, special care nursery admission, and poor neonatal adaptation when compared with infants exposed in the first and second trimesters only and control infants. In addition, birth weight was significantly lower and birth length significantly shorter in the infants exposed to fluoxetine in the third trimester.

Recommendations for clinical practice **Treatment with fluoxetine during the first trimester is associated with an increased incidence of three or more minor anomalies. Exposure during the third trimester is associated with increased rates of premature delivery, poor neonatal adaptation, lower birth weight, and shorter birth length. Major structural anomalies and spontaneous pregnancy loss were not associated with fluoxetine exposure at any time during pregnancy. The safety of other commonly prescribed antidepressants, such as tricyclic antidepressant agents, also remains in question. Family physicians managing depression in pregnant women should balance the potential risks and benefits of drug therapy.**

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