vol. XXIX, no. 1
January/February/March 2008

The Iowa PERINATAL Letter

The Rising Pre-term Delivery Rate in Iowa— Three Things We Can Do Now

Preterm birth, defined as the birth of an infant prior to 37 weeks completed gestation, continues to be the leading cause of perinatal morbidity and mortality. In 2003, over $18 billion in hospital charges were attributed to infants with any diagnosis of prematurity or low birthweight. The long-term health care visits, medications and lost productivity of parents are not included in this cost.[1] In the United States the preterm birth rate is estimated at 12.6%, or roughly 500,000 births annually. Although the rate is slightly lower in Iowa (Figure 1), this number is on the rise.[1] Iowa experienced a 22% increase in the rate of preterm birth over the ten year period from 1994-2004.

Prevention of preterm birth continues to be a priority in the United States. Healthy People 2010, a set of Federal health objectives for the new millennium, set a goal of no more than 7.6% preterm births by the year 2010. Based on the above statistics, this seems to be an unattainable goal. Before we can identify the interventions to reverse this increasing prematurity rate, let's first review the causes of prematurity.

This letter is funded by the Iowa Department of Public Health, Bureau of Family Services, and is cosponsored by The University of Iowa Carver College of Medicine, Iowa City, Iowa.

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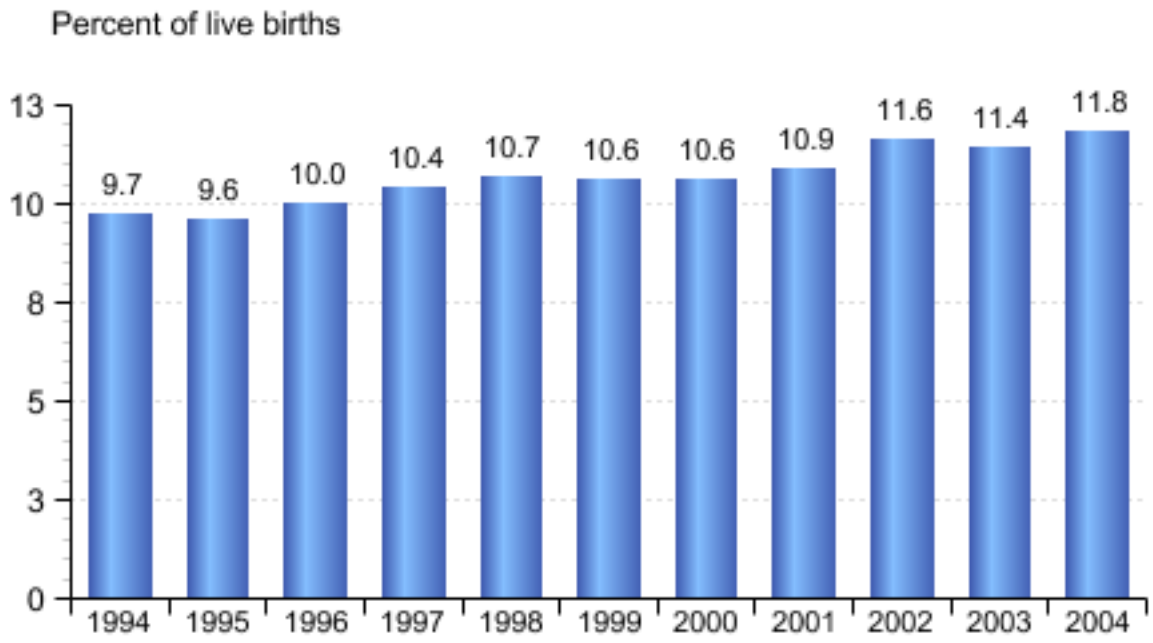

Figure 1. Premature births as percentage of total live births.[1]

Prematurity—A Complex Problem

The etiology of preterm birth is multifactorial. Spontaneous (or physiologic) preterm birth differs from induced (iatrogenic). Approximately two-thirds of the preterm births in the U.S. are spontaneous. Lockwood proposed four major etiologies of spontaneous prematurity: infection or inflammation (1), pathologic uterine distension (2), activation of the maternal-fetal hypothalamic-pituitary-adrenal (HPA) axis (3), and uterine bleeding or abruption (4).[2] Premature rupture of membranes accounts for many of the births associated with infection and inflammation; multiple gestations contribute to uterine over-distension. Maternal smoking and drug use increase the risk of placental abruption and activate the maternal-fetal HPA axis.

Iatrogenic, or medically indicated, preterm births account for the majority of the additional number of preterm births in the last ten years.[3] Figure 2 shows the yearly changes in preterm birth subtypes relative to the rate in 1989.

Prematurity—Current Treatment Recommendations

In order to have patients present at term it is important to make a timely diagnosis of preterm labor. Patient complaints of uterine pressure, vaginal discharge, cramping or low backache should prompt evaluation for uterine contractions and also a check of the state of the cervix. The goal is to make a timely diagnosis of threatened preterm labor in order that tocolytic, steroid and antibiotic therapy might be initiated without delay and when appropriate arrangements for transfer of the patient can also be made.

Tocolytics

The efficacy of tocolytics to quiet uterine contractions can, at best, be described as fair to modest. Tocolytics may be successful at inhibiting contractions for a short period of time (2 days or less). The major benefit in prolonging pregnancy with short-term tocolysis is to gain time so that corticosteroids can be administered to enhance fetal lung maturation and, if necessary, to transfer the woman to a facility with a neonatal intensive care unit. The benefits of prolonging pregnancy for longer than two days have not been clarified.

Tocolytic therapy is not without the risk of side effects to the mother. Calcium channel blockers seem to have the lowest fetal and maternal side effects. Because of this side effect profile and effectiveness, Nifedipine is now being used as the first-line tocolytic therapy at the University of Iowa. Magnesium sulfate has a significant risk of pulmonary edema and muscle weakness, without evidence to show improved neonatal outcomes. Beta-mimetics result in significant maternal hyperglycemia and cardiac toxicity, while non-steroidal anti-inflammatory drugs (NSAIDs) pose fetal effects of oligohydramnios and premature closure of the ductus arteriosus. Dual tocolytic therapy can lead to synergistic maternal side effects and should be used with extreme caution. Pregnancies continue to be at risk for premature delivery following the 48 hours of acute corticosteroid and tocolytic administration. However, maintenance of tocolytic therapy beyond this time period shows *no* prolongation of gestational age or increased birth weight at delivery in most stud-

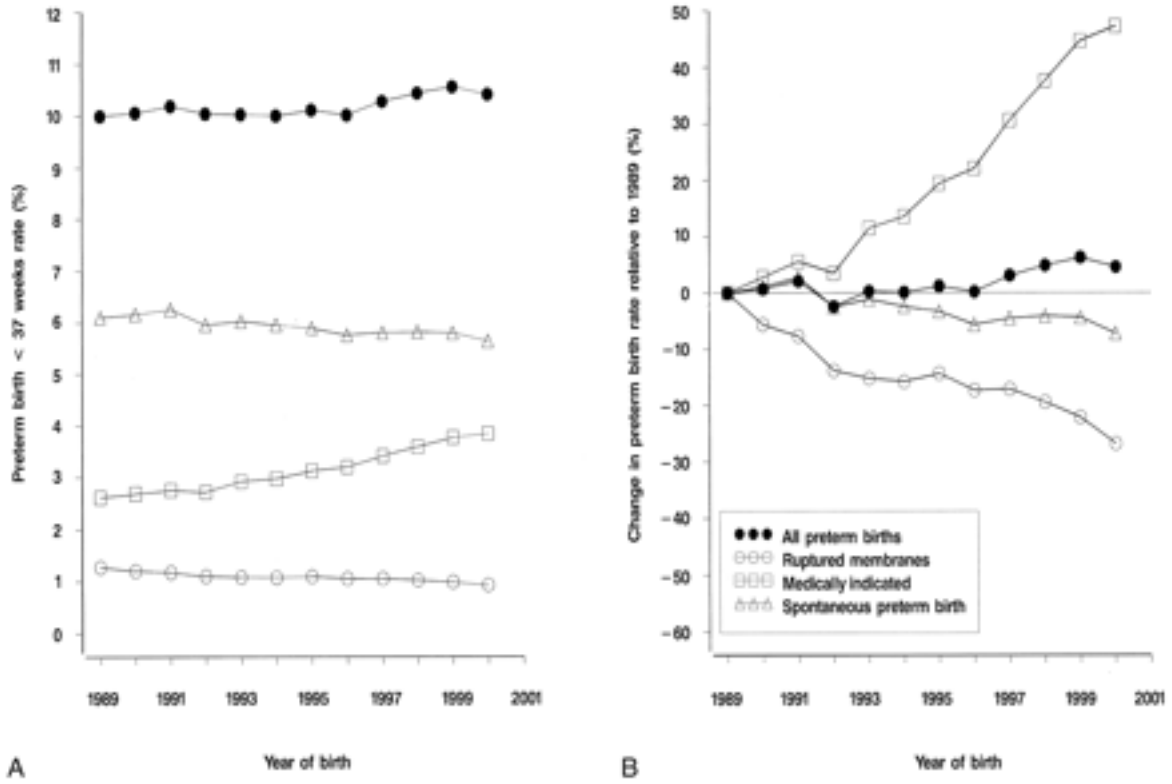

Figure 2. Yearly change in percent of preterm birth.[1]

ies. Use of tocolytic therapy beyond this initial 48 hour period therefore should not be routine.

Antibiotics

While inflammation and subclinical infection likely play a role in many cases of preterm labor, administration of antibiotics has not been effective in preventing or delaying preterm delivery.[4] The only exceptions to this rule are in the cases of asymptomatic bacteriuria and preterm premature rupture of membranes in which cases antibiotic therapy should be given. Group B strep known positivity should also be treated if the patient is in preterm labor. If the GBS status is unknown, cultures should be obtained and then initiation of prophylaxis should occur until the culture results are known. Bacterial vaginosis (BV) has been studied extensively due to its association with increased risk of preterm delivery. However, there have been conflicting data on whether treatment of BV will decrease the risk of premature delivery. Based on the evidence available to date, it does not seem that treatment will change a woman's risk for early delivery.[4] Currently, neither ACOG nor the CDC recommends screening asymptomatic women for BV.

Corticosteroids

Corticosteroids accelerate fetal pulmonary maturity by increasing surfactant manufacturing and release. For women in spontaneous premature labor, or those whom are expected to have an iatrogenic premature delivery, the benefits of antenatal corticosteroids are quite remarkable. Reductions in neonatal mortality, respiratory distress syndrome (RDS) and intraventricular hemorrhage (IVH) are well-demonstrated over a broad gestational age range (24 to 34 weeks).[5] These advantages are seen regardless of maternal race, maternal age or fetal gender. In the presence of premature rupture of membranes, antenatal corticosteroids have been shown to have benefit between 24 and 34 weeks gestation, mainly due to a reduction of RDS, IVH and neonatal death. The greatest benefit of steroids has been shown to occur in the 7 days following administration, but some benefit occurs within the first 24 hours. Either betamethasone (two doses) or dexamethasone (four doses) can be used. Although there has been some concern that betamethasone should be used preferentially due to its reduction in both mortality and periventricular leukomalacia, ACOG has not found sufficient evidence to recommend one treatment over the other.[6]

Whether antenatal corticosteroids lead to an increased risk of infection for either the mother or neonate is still unclear. In cases of fulminant maternal infection or chorioamnionitis, administration of corticosteroids would not be recommended. However, in most other cases, the risks associated with prematurity are much greater than the risk of neonatal infection. Multiple courses of administration are *not* recom-

mended, due to the increased risk of low birth weight and fetal adrenal suppression.[7] A single repeated course of corticosteroids may offer some improvement in neonatal pulmonary function; however, more investigation is needed to determine whether the benefit outweighs the risk. In follow-up studies of children up to age twelve, there was *no* evidence to indicate that antenatal corticosteroids adversely affected physical or neurologic development.

Prematurity—A Preventable Problem?

Although preterm birth is multifactorial, there are a few interventions that would benefit specific obstetric populations to minimize their risk of preterm delivery. We recommend three practices that will have a positive impact on the increasing pre-term delivery rate in Iowa; (1) adopt a zero tolerance policy for any elective delivery before 39 0/7 weeks based on good OB dating, (2) utilize Progesterone therapy in woman who have a history of pre-term birth, and (3) increase our efforts to diminish exposure to cigarette smoke, both primary smoke and second-hand smoke.

(1) Adopt a zero tolerance policy for any elective delivery before 39 0/7 weeks based on good OB dating.

This is an area where we as obstetricians may be able to intervene to decrease the prematurity rate. The maternal morbidity associated with a pregnancy complication must be significantly serious to necessitate a delivery prior to 39 weeks gestation. Temperature instability, increased risk of infection and poor feeding habits are issues facing infants born between 37 and 39 weeks gestation. Significant brain and neurologic development continue to occur in the last month of pregnancy, with the fetal brain nearly doubling in weight from 35 to 40 weeks gestation.[8] The confirmation of lung maturity through amniocentesis can minimize the risk of respiratory distress syndrome, but fetal lung maturity testing does not assess for any of the other risks of prematurity. Although the risk to the individual infant may be small, given the increasing number of "late" (34 to 36 6/7 weeks gestation) preterm deliveries, the overall impact to society is large. Increased neonatal intensive care admissions and longer hospital stays for late preterm infants are a significant cost to the medical system. Data supporting the increased neonatal morbidity associated with elective repeat Cesarean prior to 39 weeks was presented at the national meeting for the Society for Maternal Fetal Medicine in February 2008. This data is expected to be published soon.

The ACOG Technical bulletin on induction of labor lists only a few maternal indications for induction prior to 39 weeks gestation (Figure 3).[9] With adequate surveillance and treatment, both chronic hypertension and diabetes (pre-gestational or gestational), can often be managed until 39 weeks gestation. Repeat Cesarean sections should be completed at 39 weeks or after, unless a prior Classical Cesarean was performed. A woman with contractions prior to 39 weeks should clearly be in labor (cervical change *with* contractions) prior to proceeding with a repeat Cesarean. The desire to avoid uterine rupture is understood, but this risk is low (approximately 0.7%) for women with a prior low transverse Cesarean section in spontaneous labor.[10]

Placental abruption
Chorioamnionitis
Fetal demise
Premature rupture of membranes
Postterm pregnancy
Maternal medical condition (diabetes, renal disease chronic or gestational hypertension)
Fetal compromise (severe intrauterine growth restriction, isoimmunization
Preeclampsia, eclampsia

Figure 3. Indications for Induction of Labor

As physicians we must be honest about our indications for inductions that occur at any time in pregnancy, but particularly if those inductions occur before 39 weeks. Some examples that we have encountered as the Iowa Statewide Perinatal Care Team travels the State of Iowa include:

Example 1: A patient was scheduled for induction after a "deceleration of the fetal heart rate" was seen on NST in the office during her routine prenatal visit. But the induction was scheduled for the next day with no intervening testing of the fetus. Obviously this would not be the appropriate course of action if a deceleration had been seen. The patient should have been sent directly to L&D for further monitoring and assessment. If further decelerations are seen, immediate delivery may be warranted. Having the patient show up the next morning for a scheduled induction is not appropriate if a deceleration had really been documented the previous day.

Example 2: The patient is being induced for "a touch of the pressures" or "possible mild preeclampsia." However, no work up for PIH or preeclampsia is ever done, no 24 hour urine and no preeclampsia laboratory evaluation. Preeclampsia and/or PIH may be legitimate reasons for induction prior to 39 weeks, but the diagnosis must be supported by the medical record.

Example 3: We have also observed cases where the L&D personnel are given an indication for the induction, but when the admitting nurse asks the patient why they are being induced, the patient has no idea, and says something to the effect, "I don't know, the doctor just told me to show up today for induction." Of course this is suggestive of poor doctor-patient communication. If we can see through these attempts

in our brief review of records, in case of a bad outcome, a plaintiffs expert witness, who gets paid by the hour and therefore has no motivation to do a quick review, will clearly see through these inappropriate attempts to justify an early induction. We must practice safe, good and honest medicine, not only for our patients safety but for our integrity. You can imagine the guilt that will be felt by both the healthcare provider and the mother if there is a bad outcome after an inappropriate early induction that was performed for social reasons alone.

(2) Utilize Progesterone therapy in woman who have a history of pre-term birth.

Women with a history of preterm delivery are at two to three times the risk of having a recurrent preterm delivery. For these women another option is available to decrease their risk of prematurity—17 alpha-hydroxyprogesterone caproate (17-P). The exact mechanism by which 17-P works is not clearly understood but it is thought to be related to a reduction of gap junction formation and therefore decreased uterine contractions.[11] It has recently been proposed that its effect also may be anti-inflammatory in nature and that it may preserve cervical integrity. Initially studied as a 250 mg weekly injection, 17-P was found to decrease the rate of preterm delivery (less than 37 weeks) from 55 % in the placebo group to 36% in the treatment group.[12] In addition, infants of the treatment group were significantly less likely to have necrotizing enterocolitis, intraventricular hemorrhage or need supplemental oxygen. Administration of 17-P was initiated at 16-20 weeks gestation in the initial study. Although this is when we begin administration at UIHC, the optimal timing to initiate therapy has not been well-established.

Follow-up studies have evaluated the use of 17-P in differing routes of administration and study populations. Since many women would like to avoid injections and because 17-P is not widely marketed by any particular pharmaceutical company, other routes of administration have been investigated. Prophylactic administration of progesterone in the form of a vaginal suppository (100 mg qhs) was found to significantly reduce the risk of prematurity (by approximately 50%) in women who had had a prior preterm delivery.[13] Although this may be a more convenient form for patients due to self-administration, it is not widely available and must be formulated by individual pharmacies. A study is currently underway to evaluate the use of vaginal progesterone suppositories in women with a history of prior preterm birth, but with normal cervical lengths during the current pregnancy. For women with no history of a preterm birth, but a shortened (≤15 mm) cervix, it appears that progesterone suppositories may be beneficial.[14] As for twin gestations, treatment with prophylactic 17-P does not seem to reduce the risk of preterm delivery.[15] This is likely due to the different mechanism (uterine over distension) to which many twin premature deliveries are thought to be attributed. Currently, ACOG recommends that the use of progesterone supplementation in pregnancy to prevent preterm birth be restricted to women with a history of a prior spontaneous preterm delivery.[16] However, the ideal population, route and timing of progesterone therapy are yet to be confirmed.

(3) Increase our efforts to diminish exposure to cigarette smoke, both primary smoke and second-hand smoke.

Although preterm birth is multifactorial, there are a few interventions that would benefit specific obstetric populations to minimize their risk of preterm delivery. In Iowa, 23.2% of childbearing aged women smoke tobacco (March of Dimes website). Although fewer women smoke during pregnancy, efforts at smoking cessation could still offer significant benefits. Not only would the risk of preterm delivery be decreased by approximately 17%, but the complications of low birth weight, intrauterine fetal demise, neonatal death, premature rupture of membranes, placental abruption, and placenta previa would be significantly reduced as well.[17,18]

Iowans have an advantage when attempting to quit smoking. Quitline Iowa is a statewide toll-free smoking cessation hotline at 866-U-CAN-TRY (866-822-6879). This service is available 8 a.m. to midnight, seven days a week. Staffed by trained counselors from the Iowa Tobacco Research Center, Quitline Iowa offers callers state-of-the-art smoking cessation services over the phone. Callers also can request free materials to be sent in the mail, or referrals to smoking cessation resources in their community, including support groups, clinics, and consultants.

Environmental exposure to smoke is also associated with adverse pregnancy outcomes, including preterm delivery.[19,20] Iowa currently has no statewide policy regarding smoking. Rather, the law allows most business owners to choose their own smoking policies. Only recently (July 2006) did the University of Iowa Hospitals and Clinics campus become "smoke-free," with the whole campus becoming smoke-free on January 2009. Our patients could benefit from state and hospital policies to limit their exposure to tobacco smoke in public places. The Iowa legislature has made the 2008 year the "Year of Health" and as such will consider several pieces of legislation this year dealing with various health issues. One of these pieces of legislation is a bill that would ban smoking in public buildings and workplaces. We support and encourage passage of the "Smokefree Air Act."

Progesterone Supplementation	
Who?	Women with a history of ≥1 spontaneous preterm delivery ? Possibly women with a shortened cervix NOT twins NOT current preterm labor
When?	Start: 16-20 weeks gestation End: 36 weeks gestation
How?	250 mg IM weekly OR 100 mg vaginal suppository nightly

Prematurity—An Important Problem

Preterm labor is a multifactorial syndrome with complex and incompletely understood pathophysiology. This complexity challenges our efforts for prevention. While there are subpopulations of women for whom preterm delivery can be prevented, it remains important to delay delivery of very preterm infants whenever possible. Research efforts will continue to guide our therapies as greater understanding of the process is gained. Until we learn otherwise, we should continue to promote smoking cessation for all of our patients and offer 17-P to those with a history of preterm delivery.

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References:

1. March of Dimes website, January 2008. www.marchofdimes.com/peristats
2. Lockwood, CJ. Preventing premature delivery – no easy task. *N Engl J Med.* 2002 Jan 24;346(4):282-4.
3. Anath, CV and AM Vintzileos. Epidemiology of preterm birth and its clinical subtypes. *J Matern Fetal Neonatal Med* 2006 Dec 19(12): 773-782.
4. Vidaeff AC and SM Ramin. From concept to practice: The recent history of preterm delivery prevention. Part II: subclinical infection and hormonal effects. *Am J Perinat* 2006; 23: 75-84.
5. NIH consensus statement. 1994 Feb 28;12(2):1-24.
6. ACOG Committee Opinion. Number 273. May 2002.
7. Wapner RJ et al. *Am J Obstet Gynecol*. 2006 Sep;195(3):633-42.
8. Guihard-Costa AM and JC Larroche. Differential growth between the fetal brain and its infratentorial part. *Early Hum Dev.* 1990 Jun 23(1): 27-40.
9. ACOG Practice Bulletin. Number 10. November 1999.
10. Landon MB et al. Maternal and perinatal outcomes associated with a trial of labor after prior cesarean delivery. *N Engl J Med.* 2004 Dec 16;351(25):2581-9.
11. Vidaeff, AC and SM Ramin. From Concept to Practice: The recent history of preterm delivery prevention. *Am J of Perinatology* 2006; 23: 75-84.
12. Meis, PJ et al. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. *N Engl J Med* 2003 Jun 12;348(24): 2379-2385.
13. de Fonseca EB et al. Prophylactic administration of progesterone by vaginal suppository to reduce the incidence of spontaneous preterm birth in women at risk: A randomized placebo-controlled double blind study. *Am J Obstet Gynecol* 2003; 188: 419-424.
14. Fonseca EB et al. Progesterone and the risk of preterm birth among women with a short cervix. *N Engl J Med* 2007; 357: 462-69.
15. Rouse DJ et al. A trial of 17 alpha-hydroxyprogesterone caproate to prevent prematurity in twins. *N Engl J Med* 2007; 357: 454-61.
16. ACOG Committee Opinion. Number 291. November 2003.
17. U.S. Department of Health and Human Services. The Health Consequences of Smoking: A Report of the Surgeon General—2004. Centers for Disease Control and Prevention, Office on Smoking and Health, Atlanta Georgia, May 2000.
18. Kyrklund-Blomberg, N, Granath, F and S Cnattingius. Maternal smoking and causes of very preterm birth. *Acta Obstet Gynecol Scand* 2005; 84: 572-77.
19. Hanke, et al. Passive smoking and pregnancy outcome in central Poland. *Human & Experimental Toxicology* 1999; 18: 265-71.
20. Guglielmina F., et al. Preterm delivery and exposure to active and passive smoking during pregnancy a case-control study from Italy. *Paediatric and Perinatal Epidemiology*, 2007; 21: 194-200.

MARK YOUR CALENDARS!

WHAT: 34th Annual Iowa Conference on Perinatal Medicine

WHEN: April 9-10, 2008 (Wednesday-Thursday)

WHERE: West Des Moines Marriott Hotel

This annual conference is designed to provide state-of-the-art information on obstetric and newborn care practices. To view and print the conference brochure that includes the registration form go to: *http://www.idph.state.ia.us/hpcdp/statewide_perinatal_care.asp*

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