

Association Between Antenatal Cytokine Production and the Development of Atopy and Asthma at Age 6 Years

C. Macaubas, N. H. de Klerk, B. J. Holt, C. Wee, G. Kendall, M. Firth, P. D. Sly, and P. G. Holt

Telethon Institute for Child Health Research and Centre for Child Health Research, Faculty of Medicine and Dentistry, University of Western Australia, Perth, Australia

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ABSTRACT

There is mounting evidence that antenatal factors could be important in children who develop atopy and asthma. Immunologic processes appear to operate in early infancy when challenged by exposure to environmental allergens. One possible mechanism is an alteration in cytokines, which are produced in the placenta throughout gestation and serve to protect the placenta by controlling local immunologic events. The investigators measured levels of several cytokines in cord blood in a prospective birth cohort of 407 children. They included interleukins 4, 5, 6, 10, 12, and 13; interferon- γ ; and tumor necrosis factor- α (TNF α). At age 6 years, 34% of the study group had been diagnosed with asthma, 21% currently had asthma, and 40% had 1 or more positive skin-prick tests. The most commonly detected cytokines were interleukins 4 (73%), 6 (69%), and 13 (46%) of cord blood samples, and interferon- γ (37%). Higher levels of interleukins 6 and 10 were associated with perinatal stress as reflected by the need for assisted delivery and lower Apgar scores. There was, however, no relationship between cytokine levels and pregnancy complications that could correlate with chronic fetal stress. Maternal smoking during pregnancy correlated with lower cord blood levels of interleukin 4 and interferon- γ , and also with a higher risk of wheezing at age 6. Higher concentrations of interferon 4, interferon- γ , and TNF α were related to a lower risk of physician-diagnosed asthma and atopy at age 6 years. This study provides evidence of attenuated production of cytokines characteristic of peripheral blood T cells in infants at risk of asthma and atopy. The genetic factors determining the expression of peripheral blood T cells in atopic children could also control cytokine production by placental trophoblasts. In addition, cytokine production could be sensitive to adverse environmental exposures such as maternal smoking during pregnancy.

EDITORIAL COMMENT

(The rate of asthma in children is increasing; the causes for this increase are not fully known. In a prospective birth cohort of 407 children monitored for atopy and asthma outcomes at age 6 years, Macaubas et al. analyzed cryopreserved cord blood serum samples for interleukins (ILs) 4, 5, 10, 12, and 13, interferon γ , and tumor necrosis factor α (TNF α). Detectable cord blood concentrations of IL-4 and interferon γ were associated with a lower risk of physician-diagnosed asthma and atopy outcomes at 6 years. Maternal smoking was associated with higher risk of both wheezing at 6 years and

lower concentrations of IL-4 and interferon γ in cord blood. The authors concluded that the mechanism underlying the attenuated IL and interferon response in the fetal placental unit caused by maternal smoking is a target for developing preventative antenatal environmental measures related to asthma (Lancet 2003;362:1192). Yet another reason to urge our patients not to smoke in pregnancy and beyond!

The cause or causes of atopic asthma are complex and multifactorial. The related importance of genetic and antenatal environment factors remains unclear at this time. Cytokines

have an important role in controlling the functional maturation of the developing fetal immune system and its postnatal response against allergens and pathogens.

In an editorial to the article abstracted here, Holberg and Halonen suggest that cord blood differences of cytokine production reflective of fetal/placental unit function versus maternal influences should be viewed with caution, because other possibilities must be considered, including exposure to environmental toxins, intrapartum events, and genetic causes. Maternal gene variants favoring acquisition of smoking habit and the maternal cytokine alteration could also be inherited by the child. However, it does give us another reason to inform women not to smoke (Lancet 2003;362:1166).

The cytokine expressed in normal pregnancy is T-helper-2, which could protect the fetus from rejection. In contrast T-helper-1 is involved in cell-mediated toxicity and has been linked to spontaneous abortion and intraamniotic infection. These cytokines are increased and expressed as proinflammatory cytokines and chemokines in amniotic fluid, maternal serum, or cervical vaginal fluid. This proinflammatory response is an important link between maternal infection and neonatal morbidity.

Genetic predisposition could increase $\text{TNF}\alpha$ and be related to preterm premature rupture of the membranes. Recent data have demon-

strated that women who are genetically predisposed to increased $\text{TNF}\alpha$ production will more likely develop clinical infection during labor (Simhan HN, et al. Obstet Gynecol 2003; 102:162).

To examine the fetal IL expression by the cultured placenta cells, Williams et al. measured the production of IL-13. Term babies with a parental history of atopy with atopic symptoms by 3 years of age produced significantly lower concentrations of IL-13 when compared with babies with no parental history of atopy. The authors concluded that babies at risk for atopic disease in infancy displayed defective IL-13 production at birth as expressed in cultured placental cells. This could represent an inherent immaturity in the development of T cell cytokine response in babies at genetic risk for atopy. Normal pregnancy, irrespective of atopic status, is associated with the production of appreciable quantities of IL-13 initially by the placenta and subsequently by the fetus; and this was not seen in offspring with a parental history of atopy (J Allergy Clin Immunol 2000;105:9951).

Genetic mechanisms might not only determine the characteristic cytokine phenotype of the T cells in atopic children, but could control cytokine production by the fetal/placental unit. Both the fetus and the placenta might be sensitive to adverse environment exposure such as maternal smoking.—RCC)

Venous Thromboembolism During Pregnancy: Clinical Suspicion Warrants Evaluation

Jeffie S. Refuerzo, Jill L. Hechtman, Mark E. Redman, and
Janice E. Whitty

Division of Maternal Fetal Medicine, Department of Obstetrics and Gynecology, Wayne State University,
Detroit, Michigan

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ABSTRACT

Venous thromboembolism (VTE) remains an important cause of maternal deaths. Early detection and prompt treatment are critical, but many of the clinical signs of pulmonary embolism (PE) are similar to the physiological changes that take place in the peripartum period. This retrospective study focused on 70 patients, among approximately 26,000 deliveries, who underwent evaluation for either PE or deep venous thrombosis (DVT). Approximately one fourth of these women did in fact have a confirmed venous thromboembolic event. PE was diagnosed in 10 of them and DVT in 8. The respective incidence rates were 0.38 and 0.31 per 1000 deliveries. VTE was diagnosed before delivery in 44% of instances and postpartum in 56%. None of the evaluative procedures caused maternal death or complications. Patients with PE had a higher cesarean section rate than those with DVT. All women with a history of VTE were receiving anticoagulant therapy at the time VTE was suspected. Without exception, anticoagulant therapy was initiated at the time VTE was clinically suspected and before diagnostic testing began. There were no major differences in symptoms and signs between women with and those without PE. Patients with DVT more often had swelling and pain in the legs. Of 52 women whose tests were negative for VTE, 56% received an alternative diagnosis. The most common diagnoses were exacerbation of asthma, pneumonia, and pulmonary edema. PE should be considered in any pregnant woman with pulmonary symptoms, even if other possible causes are present. A lack of definitive symptoms and signs of VTE warrants thorough evaluation for DVT or PE.

EDITORIAL COMMENT

(In 2003, the U.S. maternity mortality rate was 8 to 10 per 100,000 white women and 30 per 100,000 US black women. (MMWR Morb Mortal Wkly Rep 2003;52:1-8). Venous thromboembolism (VTE) occurs in 0.5 to 3 per 1000 pregnancies. Pulmonary embolism has replaced hemorrhage, hypertensive disorders, infection, and cardiomyopathy as the leading cause of mortality. Every obstetrician-gynecologist must keep a heightened awareness of the signs and symptoms of possible VTE during pregnancy or postpartum. A high clinical suspicion and complete diagnostic workup along with early detection and prompt treatment are important in preventing severe morbidity and mortality.

To determine the signs, symptoms, and clinical outcomes of VTE during pregnancy, Refuerzo et al. retrospectively reviewed the course of 70 patients from 1997 to 2001. Of the 70 patients as-

essed, 18 (25.7%) had confirmatory diagnostic testing. Pulmonary embolism (PE) was diagnosed in 10 patients (14.3%) and deep venous thromboembolism (DVT) in 8 (11.4%). In patients with PE, there was no difference in the rate of shortness of breath, chest pain, cough, apprehension, hemoptysis, leg swelling, or leg pain compared with those without PE. In those patients with negative diagnostic tests, an alternative diagnosis was confirmed in approximately 50% of patients; 17.3% had asthma, 15.4% were diagnosed with pneumonia, and 15.4% had pulmonary edema. Of the patients with positive diagnostic testing, 30% had a concurrent condition contributing to the pulmonary symptoms. The authors concluded that the lack of definitive signs and symptoms of thromboembolic disease during pregnancy mandates a complete evaluation of the patient (J Reprod Med 2003;48:767).

A review of thromboembolism in pregnancy published in 2000 by ACOG recommended compression ultrasound and impedance plethysmography to evaluate the risk of VTE in pregnancy. If these noninvasive tests are negative, venography with abdominal wall shielding could be considered. When there is a suspicion of a PVT, the use of venography along with magnetic resonance imaging could be the modalities of choice, but the results from MRI are still not well-defined in a pregnant patient. If there is a suspicion of PE, the ventilation-perfusion (VQ) scan results in minimal radiation exposure to the fetus. However, any VQ scan outcome other than high probability or normal requires further testing because of the insufficient accuracy. If the noninvasive testing reveals proximal DVT, anticoagulation should be initiated. If the results of these tests are negative, but the clinical suspicion is high, then pulmonary angiography or spiral computerized tomography (CT) should be considered; CT could detect abnormalities other than PE as responsible for symptoms such as pleural effusion, pulmonary consolidation, and masses (ACOG Practice Bulletin, Thromboembolism in Pregnancy. Washington, DC; 2000:19). Although there is enthusiasm for using D-dimer values in the diagnosis of VTE, the value of this test has not been confirmed for pregnant patients in whom D-dimer values are normally high (Brockenstedt P. *N Engl J Med* 2003;349:120).

To determine the risk factors for DVT and PE during pregnancy or postpartum, Danilenko-Dixon et al. performed a population-based control study from 1966 to 1990. In a multivariate analysis, smoking and prior superficial vein thrombosis were independent risk factors for DVT or PE during pregnancy or postpartum for approximately 30% of the 90 patients studied. The authors believe that venous thromboembolism prophylaxis could be warranted for pregnant women with a history of a superficial vein thrombosis. Smoking cessation should be recommended, especially during pregnancy and the postpartum period (*Am J Obstet Gynecol* 2001;184:104). Other factors associated with an increased risk of DVT during pregnancy and postpartum are multiparity, preeclampsia, cesarean delivery, preterm delivery, and postpartum hemorrhage.

Many times, the normal physiological changes associated with pregnancy such as leg edema, swelling, and mild tachycardia complicate the clinical suspicion of VTE. Only by keeping a high clinical index of suspicion of VTE and being persistent in ruling out a thromboembolic phenomenon can patient safety be ensured. It is recommended that all patients suspected of having a VTE should be started on anticoagulation therapy immediately and a complete evaluation should be performed to confirm or exclude the diagnosis.—RCC)

Hot Tub Use During Pregnancy and the Risk of Miscarriage

De-Kun Li, Teresa Janevic, Roxana Odouli, and Liyan Liu

Division of Research, Kaiser Foundation Research Institute, Kaiser Permanente, Oakland, California

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ABSTRACT

Animal studies suggest that hyperthermia leads to fetal resorption, abortion, and fetal death. Little is known, however, about the effects of elevated body temperature in humans. This study was an attempt to learn whether using a hot tub or whirlpool bath during pregnancy heightens the risk of miscarriage before 20 weeks gestation. The prospective,

population-based cohort study enrolled 1068 women during the years 1996 to 1998. In-person interviews were conducted early in pregnancy. Women who used a hot tub or Jacuzzi while pregnant had a higher socioeconomic status than nonusers and were more likely to be 30 years of age or older, to be white, and to have smoked, consumed alcohol, or used recreational drugs. Users also tended to take multivitamins and appeared to have exercised more strenuously than nonusers since the last menstrual period. Nonusers were likelier to have had more than 1 past miscarriage. The prenatal use of alcohol or recreational drugs was not associated with the risk of miscarriage in this population. After adjusting for many potential confounding factors, women using hot tubs or Jacuzzis while pregnant were twice as likely as nonusers to have a miscarriage (adjusted hazard ratio, 2.0; 95% confidence interval, 1.3–3.1). There was some indication that higher water temperatures could further increase the risk of miscarriage, but maternal fever of 100°F or higher during pregnancy was not related to the chance of miscarrying. Increasingly frequent use and use at a very early gestational age might also be associated with miscarriage, although none of these associations were statistically significant. An increased risk of miscarriage also was evident when evaluating only women who had had 2 or more previous miscarriages or were subfertile (defined as unprotected intercourse for longer than 12 months without becoming pregnant). The relationship between prenatal exposure and the risk of miscarriage was stronger in this subpopulation. These findings suggest that using a hot tub or Jacuzzi in early pregnancy is associated with an increased risk of miscarriage.

EDITORIAL COMMENT

(In a 1996–1998 population-based prospective cohort study, Li et al. determined the risk of miscarriage after hot tub or whirlpool bath use during early pregnancy. Approximately 1000 women completed the interviews. The rate of spontaneous abortion before 20 weeks gestation occurred in 103 women. After adjusting for confounders, use of a hot tub or whirlpool bath after conception was associated with a 2-fold increased risk of miscarriage (adjusted hazard ratio, 2.0; 95% confidence interval [CI], 1.3–3.1). The risk seems to increase with frequency of use, 1.7 for less than once a week, 2.0 for once a week, and 2.7 for more than once a week; the risk is 2.3 with initial use in the first 4 weeks from the last menstrual period (LMP) and 1.5 if initial use is after 4 weeks from the LMP (AM J Epidemiol 2003;158:931). There are few studies of hyperthermia on human pregnancy outcome; the risk of external source of heat and maternal hyperthermia and miscarriage remains controversial. Most studies focus on fever in pregnancy secondary to infection; it is difficult to ferret out the effect of fever as opposed to infection.

In a commentary on the article abstracted here, Hertz-Picciotto and Howards believe that the study had limitations. In addition to a low response rate (39%), data for early gestation weeks were sparse and might not represent the population; most cases were interviewed after they miscarried, and the association hinges on the subgroup of these women who miscarried.

The accuracy of determining gestational age was also questionable (Am J Epidemiol 2003;158:938).

To determine whether fever in early pregnancy is a risk factor for fetal death in humans, Andersen et al. interviewed 24,040 women and obtained information on the number of fever incidents during the first 16 weeks gestation. Miscarriage or stillbirth occurred in 1045 pregnancies (4.8%). During the 16 weeks, 18.5% of women experienced at least 1 episode of fever. However, the authors found no association between fever in pregnancy and fetal death after adjusting for known risk factors for fetal death. This finding was consistent irrespective of measured maximum temperature, duration, and number of fever incidents, or the gestation time of the fever incident. The authors believe they found no evidence that fever in the first 16 weeks gestation was associated with the increased risk of fetal death in clinically recognized pregnancies (Lancet 2002;360:1552; Obstet Gynecol Surv 2003;58:293).

Hyperthermia in experimental animals has been associated with reabsorption of embryos, fetal death, and malformations related to the central nervous and cardiovascular systems. The results in animal experiments suggest that similar effects might occur in humans. However, fever in the early part of pregnancy and its association with spontaneous miscarriage remains controversial. In a hospital-based case-control study, Kline et al. found a significant

odds ratio (OR) for maternal fever preceding spontaneous abortion in chromosomally normal pregnancies (adjusted OR, 5.47, 95% CI, 2.73–10.96 for fever of 37.8°C or higher within the month before abortion) (Am J Epidemiol 1985;121:832).

Spontaneous abortion is a difficult subject to study. Even in prospective studies in which women are enrolled early in pregnancy, some selection bias might occur. In an editorial to the study mentioned here by Anderson et al., I noted that a prospective study of fever in pregnancy would be hard to conduct. Therefore, any information received must be taken with a grain of salt. Pregnant women should not categorically conclude that fever in pregnancy is of no serious consequence, as was suggested in the Anderson study. Pregnant women who experience a fever of 38.9°C of short duration early in pregnancy might not be at an increased risk of

spontaneous abortion and/or fetal malformation. However, women who experience fever of more than 38.9°C that lasts more than 24 hours in early pregnancy are at an increased risk of a major central nervous system malformation. Thus, all fever in pregnancy should be reported to the physician; if fever persists, then appropriate examinations and laboratory analysis should be done.

Although the use of a hot tub or whirlpool was associated with the risk of miscarriage, there was no information on the use of a sauna or steam baths. This is the first reported association between exposure to an external heat source and an increased risk of miscarriage. More precise determination of gestational age, greater patient participation, and confirmatory studies in different populations are needed before we accept the hypothesis of fetal harm related to hot tub exposure in early pregnancy.—RCC)

Children Conceived Using Intracytoplasmic Sperm Injection Do Not Have an Increased Risk of Delayed Mental Development at 5 Years of Age

G. I. Leslie, F. L. Gibson, C. McMahon, J. Cohen, D. M. Saunders, and C. Tennant

Departments of Obstetrics and Gynaecology and Psychological Medicine, University of Sydney Northern Clinical School; and the Department of Neonatology, Royal North Shore Hospital, St. Leonards, New South Wales, Australia

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ABSTRACT

Since intracytoplasmic sperm injection (ICSI) was first used a decade ago, there has been concern about possible long-term adverse effects on health, psychosocial status, and developmental outcomes. The initial controlled study of ICSI children 1 year of age, using the Bayley Mental Development Index, found an increased risk of delayed mental development compared with children conceived naturally or using *in vitro* fertilization (IVF); the relative risk was 9.2. The present study reassessed development at age 5 years using a more accurate measure of cognitive ability, the Wechsler Preschool and Primary Scales of Intelligence–Revised (WPPSI-R). Mental development was assessed in 97 ICSI, 80 IVF, and 110 naturally conceived (NC) children. They included 213 of the original cohort of 253 children. The mean age at the time of assessment was 61 months. Mean values for the WPPSI-R were within the normal range in all

3 groups, and no between-group differences were apparent. Delayed full-scale IQ scores (IQ below 85) were recorded for 5.2% of ICSI, 2.5% of IVF, and 0.9% of NC children. Normal scores were obtained for 58.7%, 61.2%, and 56.4% of children, respectively. Accelerated scores (IQ above 115) were recorded for 36.1% of the ICSI group, 36.3% of IVF children, and 42.7% of NC children. There were no significant between-group differences in any of these 3 categories. The likelihood of a delayed full-scale IQ score in the ICSI group was not significantly increased when compared with the other groups, individually or together. On multivariate analysis, the only significant and independent predictor of a below-average full-scale IQ score was a lower maternal educational level. Within the ICSI group, full-scale IQ was not related to the type of defect in paternal sperm. These findings should reassure parents of children conceived using ICSI that the procedure does not impair long-term cognitive function. The genetic influence of parental cognitive ability appears to be more important than the mode of conception.

EDITORIAL COMMENT

(In a previous insightful editorial comment, my coeditor, Dr. Jaffe, discussed the study from Western Australia that found an increased incidence of major congenital anomalies among children conceived using intracytoplasmic sperm injection (ICSI; 8.6%) as compared with children conceived naturally (4.2%) (Hansen M, et al. *N Engl J Med* 2002;346:725; *Obstet Gynecol Surv* 2002;57:517). The incidence of anomalies among children conceived by standard in vitro fertilization (IVF) was (9.0%), essentially the same as that for the ICSI group. There was no telltale grouping of anomalies in the children conceived by assisted reproductive technologies (ART), and as Dr. Jaffe pointed out, there was no clearcut explanation for the increased rate of birth defects. Importantly, in regard to patient counseling about ICSI, he drew attention to the fact that 91% of children born following the ART methods in this study had no anomalies.

The study abstracted here, also from Australia, evaluated developmental outcomes at 5 years of age in children conceived by ICSI, IVF, or naturally. After correcting for a number of confounding variables (parental education, preterm birth, multiple gestation, family history of developmental problems, and so on), there were no significant differences in mean IQ among the 3 groups of children. Regarding the children conceived by ICSI, there was no association found between the child's IQ and any abnormality in the paternal sperm.

Mental development was tested at 1 year of age and 5 years of age in the children in this study. An interesting finding was that at 1 year, there was a significantly higher incidence of delayed development among those children con-

ceived by ICSI as compared with both the IVF group and the naturally conceived groups. At 5 years of age, the number of children conceived by ICSI with cognitive delay was significantly lower than at 1 year of age, and the incidence of developmental delay was no different than in the 2 control groups. It is not certain whether this finding could be accounted for by a natural improvement in intelligence or some vagary of the testing procedures used at the 2 testing periods. However, the lesson to be learned from this is that developmental evaluation at 1 year of age might not be an accurate assessment of a child's potential, and prognosis based on 1-year testing results should be offered cautiously. Other studies of development outcome in ICSI-conceived children have shown conflicting results, but these studies have all assessed the children at less than 2 years of age.

Another finding in this study was that parental cognitive ability is a more important factor in a child's developmental outcome than is the method of conception. This finding is consistent with most of the research on developmental outcomes in children, in which the parents' cognitive development, whether the result of genetic or environmental factors, is usually the major determinant of a child's developmental outcome.

The results of this study should be reassuring for couples who are considering ICSI as a solution to a problem with fertility. Nevertheless, the slightly increased risk of birth defects in ICSI-conceived children should not be overlooked. I agree with Dr. Jaffe's recommendation that there should be clearcut justification for the use of ART as an alternative to spontaneous and less invasive means to conceive.—WAB)

Fetal Gasping of the Umbilical Cord and Perinatal Outcome

Dubravko Habek, Jasna Cerkez Habek, Ante Barbir, Mira Barbar, and Paula Granic

Department of Obstetrics and Gynecology Clinical Hospital, Osijek, Croatia; and Clinical Hospital Rebro, Zagreb, Croatia

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ABSTRACT

The grasp reflex (GR) is one of the "primitive" reflexes characteristic of intrauterine development and early infancy. The GR is evident by 16 weeks gestation and is usually well developed by 27 weeks. Normally, the GR is no longer found in healthy term infants 3 months after birth. A GR persisting after this time is taken as a sign of a frontal lobe lesion. Fetal grasping of the umbilical cord (FGUC), noted on ultrasonography late in pregnancy, is a possible cause of fetal hypoxia secondary to occlusion of the umbilical circulation. In this retrospective study, a total of 2439 ultrasound studies were carried out in 800 pregnancies over a 2-year period. FGUC was found in 7 normal singleton pregnancies at 32 to 41 weeks gestation. It was first noted at a median gestational age of 36 weeks; the median age at delivery was 39 weeks. All measurements of the umbilical artery resistance index (URI) were increased as a result of persistent FGUC. There were marked oscillations in values of resistance in the middle cerebral artery. In 2 cases, the cerebral/umbilical was less than 1, indicating vasocentralization that presumably compensated for hypoxia. Pathologic cardiocotograms and preacidosis were observed in these cases. Two infants with pathologic cardiocotograms had the cord wound around the neck. All infants were discharged healthy from the neonatal intensive-care unit except for these 2, who had dystonia and mild motor deficit reflecting peripartum hypoxia. Intermittent FGUC probably is normal, but it calls for ultrasonographic monitoring. If persistent, FGUC is not normal and could obstruct the umbilical circulation and produce hypoxia. Women with persistent FGUC should be closely monitored in the hospital.

EDITORIAL COMMENT

(This important study is the first to document the frequency of fetal grasping of the umbilical cord (FGUC) as recognized during intermittent ultrasound scanning of patients between 32 and 41 weeks gestation. The authors report 7 instances in which FGUC was noted in 800 pregnancies (0.8%). This is not the incidence of FGUC during normal pregnancy. That could only be determined by continuous ultrasound monitoring in a group of women during normal pregnancy. It is likely that FGUC is substantially higher than 0.8%. Also, the authors made an important contribution in documenting Doppler velocimetry and fetal heart rate (FHR) changes associated with FGUC, and they recorded the fetal outcomes.

Grasping is a primitive reflex of the fetus and infant, developing as early as 16 weeks of fetal life and disappearing by 3 months of postnatal age. Newborn grasping is 1 response to stress as documented by elevated plasma cortisol levels (Tan V, Zor N. *Int J Neurol Sci* 1994;74:27).

Therefore, it is likely that FGUC can be a response to hypoxia, at least in some instances. In the present study, there are not sufficient details about the sequence of FGUC related to changes in Doppler findings or FHR to draw conclusions about whether FGUC is a response to or a cause of fetal hypoxemia.

I find it difficult to imagine that the grasp of a 36-week fetus can compress to any important extent its umbilical cord, which, in the presence of normal umbilical blood flow, is a relative turgid structure. However, Petrikovsky and Kaplan have provided evidence that FGUC can effectively compress the umbilical vessels (*J Clin Ultrasound* 1993;21:642). They observed FHR decelerations associated with periodic fetal grasping of the umbilical cord at 36 weeks gestation. The FGUC was interrupted with vibratory acoustic stimulation, a procedure that has been used before as an effective measure to interrupt FGUC.

In the present study, 3 infants were delivered operatively because of FHR abnormalities, and 4 infants required neonatal intensive care for meconium aspiration syndrome. However, no infant was severely acidotic at birth and all infants had 5-minute Apgar scores of 8 or greater. One infant had evidence of a mild motor deficit thought to be caused by peripartum hypoxia, but the other 6 infants had no neurologic abnormalities.

Ultrasound imaging, especially color-enhanced imaging, has increased the interest in and knowledge about umbilical cord abnormalities and vulnerability. Sherer and colleagues have written excellent review articles summarizing the current knowledge about the clinical implications of umbilical cord abnormalities (*Obstet Gynecol Surv* 1997;52:506,515; *Am J Perinatol* 1999;16:445). Umbilical cord cysts, tumors, aneurysms, varices, knots, single umbilical artery, nuchal cord, and other abnormalities can be identified with prenatal ultrasound. The difficulty is in knowing what should the clinical response be when these abnormalities are identified before birth. Nuchal cord, which is present in 15% to 30% of pregnancies, is the most common cord "abnormality" noted by ultra-

sound. Although recognizing that something that occurs in 30% of pregnancies is not necessarily an abnormality, there is both clinical and epidemiologic evidence that the presence of a nuchal cord, especially if there is more than 1 loop, increases the risk of fetal hypoxemia, fetal death, and developmental abnormalities. The level of that risk is difficult to ascertain, as is the benefit of any intervention. Clinical managements often will be dictated by other clinical findings such as fetal growth restriction, congenital defects, placental abnormalities, abnormal Doppler findings, or ominous FHR patterns. At present, the detection of an umbilical cord abnormality should be the occasion for a more thorough search for other abnormalities rather than a cause of unmitigated alarm and a dour prognosis.

Similarly, if a fetus is found grasping its umbilical cord, additional fetal monitoring and a search for other fetal abnormalities is appropriate, especially if vibratory acoustic stimulation does not interrupt the behavior. The few reports in the literature about this fetal behavior, including the one abstracted here, and a moderate amount of common sense support a very optimistic prognosis for these situations.—WAB)

Association of Vasa Previa at Delivery With a History of Second-Trimester Placenta Previa

Karrie Francois, Staci Mayer, Cathleen Harris, and Jordan H. Perlow

Department of Maternal-Fetal Medicine, Good Samaritan Regional Medical Center, Phoenix, Arizona; and the Department of Obstetrics and Gynecology, University of Arizona, Tucson, Arizona

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ABSTRACT

Vasa previa is a rare obstetric disorder characterized by velamentous insertion of the fetal vessels over the mouth of the cervix. Reported fetal mortality estimates range from 58% to 73%. Ultrasonography has proved helpful for diagnosing this condition prenatally, improving outcomes, but little is known about any antecedent conditions that predispose to vasa previa. This study evaluated 1 possible factor, a history of second-trimester placenta previa, in 13

women presenting with vasa previa in the years 1991 through 2001. Deliveries totalled nearly 73,000 during this period. Vasa previa occurred once in every 5614 deliveries. Four control women with normal placentation were matched with each study patient. Eight of the 13 cases were detected in the third trimester by demonstrating fetal blood flow over the cervical os using pulsed color flow Doppler ultrasonography. Two other women presented at the time of amniotomy during labor with acute vaginal bleeding and subsequent fetal bradycardia. In 2 cases, the fetal vessels were palpated within the amniotic membranes during labor. One case was diagnosed after delivery, the fetus having died; torn fetal vessels were found when viewing the placenta. This woman had undergone membrane stripping during a prenatal visit at 41 weeks gestation. Three of the 13 women with vasa previa were nulliparous. Demographic features were similar in the study and control groups, although affected women tended to be older and to have undergone dilation and curettage more often than control women. Antepartum vaginal bleeding, cesarean delivery, and cesarean hysterectomy all were more frequent in study women. Two women, including the 2 with a dead fetus, were delivered vaginally. Nine of 13 women (69.2%) had placenta previa diagnosed by midtrimester ultrasonography. This was true for only 2 control women (3.8%), making the association highly significant. This retrospective study disclosed a statistically impressive relationship between vasa previa at delivery and a history of second-trimester placenta previa. Prospective studies of women with the latter condition would be of interest.

EDITORIAL COMMENT

(In a previous issue of the *Survey*, I commented on a study by Catanzarite et al. that provided encouraging information about the prenatal diagnosis of vasa previa by routine attempts to image the insertion of the cord into the placenta (*Ultrasound Obstet Gynecol* 2001; 17:109; *Obstet Gynecol Surv* 2002;57:73). Timely prenatal diagnosis of vasa previa allows for planned cesarean delivery before the onset of labor, thereby avoiding catastrophic fetal blood loss.

The prevalence of vasa previa is 1 in 2500 deliveries; consequently, a substantial number of patients must be screened by whatever method before the diagnosis will be made. The retrospective case-controlled study abstracted here from the Good Samaritan Regional Medical Center in Phoenix found a significant relationship between vasa previa (proven either clinically or by pathology) and second-trimester placenta previa documented by ultrasound. Among the 13 patients with vasa previa, 9 (69.2%) had ultrasound evidence of placenta previa, whereas second-trimester placenta previa was noted in only 3.8% of matched control patients who did not have vasa previa (odds ratio, 56.3; confidence interval, 8.9–354.1). Twelve of the 13 fetuses survived. The diagnosis was made before delivery by detection with Doppler ultrasound of fetal blood flow over the cervical os; in 2 patients, vaginal bleeding and fetal bradycardia led to the diagnosis; and in 2 patients the diagnosis was made during labor by palpation of fetal vessels within the membranes. Only 1

fetus died before the diagnosis of vasa previa was recognized. Overall, this is a remarkably good outcome for a condition that in the past has been associated with a perinatal mortality rate of 33% to 100%. The outcome in these patients confirms the impression of Oyelesse et al. in their review of vasa previa that it is, indeed, an avoidable obstetric tragedy in many cases (*Obstet Gynecol Surv* 1999;54:138).

In approximately 10% of prenatal patients, ultrasound examination will discover a placenta previa or very low implantation of the placenta in early pregnancy. Although over 90% of these patients will not have clinically diagnosed placenta previa at birth, they are at higher risk for a number of other pregnancy complications: antepartum hemorrhage, abruptio placentae, fetal growth restriction, and prematurity (Newton ER, et al. *Am J Obstet Gynecol* 1984;148:743). Vasa previa can now be added to this list. The so-called “migration” of the placenta that occurs between the second and third trimesters of pregnancy is actually a differential growth and atrophy of areas of the placenta as the uterus enlarges. In some cases, this leaves behind exposed vessels in the membranes that cover the cervical os, thus resulting in vasa previa.

In the present study, there were not sufficient data from the ultrasound reports to determine the exact distance the midtrimester placenta extended over the cervical os. Such data might help to determine if there are specific characteristics of the low implanted midtrimester placenta that predispose to subsequent vasa previa. Even without

such information, the presence of low implantation of the placenta in the second trimester should alert obstetricians that the patient is at increased

risk for vasa previa (among other things) and should enhance sensitivity to any episode of vaginal bleeding.—WAB)

Prediction of Adverse Outcome Associated With Vaginal Misoprostol for Labor Induction

M. Mutlu Meydanli, Eray Caliskan, and Ali Habral

SSK Maternity and Women's Health Teaching Hospital, Ankara, Turkey

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ABSTRACT

Misoprostol, an analog of prostaglandin E₁, promotes cervical ripening and induction of labor in term pregnancies and also stimulates uterine contractions. Debate continues about whether this agent can induce excessive uterine activity. This prospective observational study was done to identify predictors of poor outcomes in 720 pregnant women with term pregnancies who had an unfavorable cervix and a medical or obstetric indication for inducing labor. They were given 50 μ g misoprostol intravaginally every 4 hours, with a maximum of 3 doses. The mean age was 27 years, and the mean gestational age was 40.3 weeks. A single dose of misoprostol induced labor in 85% of women. Of 108 women given a second dose, 62 required a third. The failure rate was 4.2%. Approximately 13% of women required oxytocin during labor. The mean interval from induction to delivery was 11.3 hours. The rate of cesarean delivery, 22%, was similar to the institutional rate during the period of study. Birth weights averaged 3402 g. There were no infant deaths. Adverse effects were noted in 13.6% of patients. Nearly 11% required emergent cesarean section because of a nonreassuring fetal heart rate tracing. Twenty-two infants had metabolic or mixed acidemia. Adverse outcomes could not be predicted by demographic factors or the reason for inducing labor, but fetal tachycardia and tachysystole were significantly more frequent than in women with safe deliveries. On logistic regression analysis, both these states were significant predictors of an adverse outcome. The odds ratios were 3.7 and 4.8, respectively. Misoprostol is a clinically effective means of inducing labor, and it might be the only affordable prostaglandin for this purpose where resources are limited. Unless fetal tachycardia or tachysystole develops, an uneventful delivery could be expected in women given 50 μ g misoprostol.

EDITORIAL COMMENT

(Misoprostol is becoming the most commonly used method for cervical ripening and induction of labor. On April 17, 2002, the U.S. Food and Drug Administration approved a new label use of the drug for induction of labor. The reasons for its popularity and approval include ease of administration (either orally or vaginally), remarkably low cost, and a number of prospective trials demonstrating its effectiveness and relative safety. The major contraindication for its use for labor induction is in patients who have had a cesarean delivery because of a demonstrated increase in the risk of uterine scar rupture. There are still debates

about the appropriate vaginal dose for cervical ripening or labor induction (50 μ g vs. 25 μ g given), the interval between doses, the maximum total dose, and the timing of adjuvant use of oxytocin. A recent ACOG Committee Opinion recommends an initial vaginal dose of 25 μ g with dosing intervals of 3 to 6 hours (Obstet Gynecol 2003;101:1049). Studies have shown that a 50- μ g starting dose results in somewhat shorter labors, but at greater risk of uterine hyperstimulation and meconium staining of amniotic fluid, although serious maternal and perinatal complications are not increased. Compared with oral administration,

vaginal administration of misoprostol is more effective for induction of labor and associated with fewer side effects.

In the study abstracted here, the dose of misoprostol was 50 μg vaginally, repeated at 4-hour intervals; results showed that tachysystole (greater than or equal to 6 contractions in 10 minutes) and fetal tachycardia (>160 beats/min for more than 10 minutes) were significant predictors of fetal acidemia ($\text{pH} < 7.15$) and emergent cesarean delivery for nonreassuring fetal heart rate (FHR). The potential physician bias in performing emergency cesarean delivery was minimized by strict criteria for nonreassuring FHR tracings and decisions to perform cesarean delivery. As is the case for almost all other tests of fetal well-being, the sensitivity of this test was found to be low (20.4%) but the specificity was high (94.5%). In other words, the absence of tachysystole and fetal tachycardia are far more reliable predictors of a normal out-

come than their presence is of an abnormal outcome.

In this study, in which 50% of the patients were nulliparous, and all of whom had a Bishop score < 4 , a single dose of 50 μg misoprostol given vaginally was sufficient to induce labor in 85% of the patients. Although this study was not designed to determine the relative effectiveness and safety of 50 μg misoprostol as compared with 25 μg as a starting dose for induction of labor, it would have been interesting to know if the cesarean rate for nonreassuring fetal heart rate changes of 10.6% would have been lower had the starting dose been 25 μg . Although fetal tachycardia occurred in only 3% of patients and tachysystole in 6%, these might even have been lower had a lower dose of misoprostol been used. Overall, I believe this study supports the recommendation by the ACOG that the starting vaginal dose of misoprostol for induction of labor be 25 μg .—WAB)

Cerebral Palsy and Intrauterine Growth in Single Births: European Collaborative Study

Stephen Jarvis, Svetlana V. Glinalanaia, Maria-Giulia Torrioli, Mary-Jane Platt, Maria Micell, Pierre-Simon Jouk, Ann Johnson, Jane Hutton, Karla Hemming, Gudrun Hagberg, Helen Dolk, and James Chalmers on behalf of the Surveillance of Cerebral Palsy in Europe (SCPE) collaboration of European Cerebral Palsy Registers

Institute of Child Health and Department of Epidemiology and Public Health, University of Newcastle, U.K.; Universita Cattolica S. Cuore, Rome, Italy; the Department of Public Health, University of Liverpool, U.K.; Agenzia di Sanita Pubblica Regione Lazio, Rome, Italy; Centre Hospitalier Universitaire de Grenoble, Grenoble, France; the National Perinatal Epidemiology Unit, University of Oxford, Oxford, U.K.; the Department of Statistics, University of Warwick, U.K.; Queen Silvia Children's Hospital, Goteborg University, Sweden; Faculty of Life and Health Sciences, University of Ulster at Jordanstown, U.K.; and the Information and Statistics Division, National Heart Service Scotland, Edinburgh, U.K.

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ABSTRACT

In developed countries, cerebral palsy (CP) remains the most common form of severe physical disability in children. Approximately 25 years ago, the rate of CP was found to be substantially increased in low-birth-weight children, but

the cause of CP still is poorly understood. The authors report a survey of 10 European registers totaling 4503 singleton children with CP who were born in the years 1976 through 1990. The goal was to learn whether altered intrauterine growth is a pathologic factor in the origin of CP. CP was defined as a group of disorders that involve disordered movement, posture, or both as well as motor dysfunction. It is a permanent condition that can change but is not progressive. Using conventional fetal growth standards, infants born at 32 to 42 weeks gestation whose birth weight for gestational age was below the 10th percentile were 4 to 6 times more likely to have CP than were reference children with birth weights between the 25th and 75th percentiles. The increase in risk was considerably less (1.6- to 3.1-fold)—but still significant—in children whose birth weights were above the 97th percentile. The risk of CP was lowest in children whose birth weights were approximately 1 standard deviation above average. Similar findings were obtained for infants having unilateral or bilateral spasticity, and also for those who were dyskinetic or ataxic. The relationship between birth weight and risk of CP, if any, was less clear in children who were born before 32 weeks gestation. As is the case for perinatal death, the risk of CP is lowest in infants who at birth are above average weight for gestational age. However, the risk of CP increases not only when birth weight is well below normal, but also when it is well above normal. Possibly an abnormal growth pattern causes CP, or vice versa, or there could be some factor that is linked independently to both growth and the risk of CP. Conceivably, brain damage or impaired development *in utero* triggers an abnormal growth pattern through an endocrine pathway or some other mechanism. An alternative explanation is that abnormal growth renders the fetus more vulnerable physiologically, and that the brain is exposed to irreparable damage during or after delivery.

EDITORIAL COMMENT

(The causes of cerebral palsy (CP) are multifactorial: infection, coagulation defects, multiple births, prematurity, “vanishing twin episodes,” and antepartum and intrapartum uteroplacental insufficiency all have been implicated. Regarding low and high birth weight for gestational age, both ends of the spectrum have been implicated in the prevalence of CP.

To assess deviations from normal fetal growth as a possible pathologic factor in origins of CP, Jarvis et al. compared data from 10 European registries for 4503 singleton children with CP born between 1976 and 1999. Babies at 32 to 42 weeks gestation with a birth weight for gestational age below the 10th percentile were 4 to 6 times more likely to have CP than were children in a reference band between 25th and 75th percentiles. In children with a weight above the 97th percentile, the increased risk for CP was smaller (from 1.6 to 3.1) but still significant. The authors concluded that the risk of CP increases when birth weight is above the 97th percentile. Whether birth weight above the 97th percentile is the cause or the consequence remains to be determined (Lancet 2003;362:1106).

A case-control study by Badawi et al. identified a significant increase in the risk for encephalopathology with each week after 39 weeks gestation. Compared with newborns delivered at 39 weeks, the adjusted relative risk increased to 1.41 at 40 weeks, 3.34 at 41

weeks, and 13.2 at 42 weeks gestation (BMJ 1998;317:1549). However, data for gestational age alone must be taken with a grain of salt. Many studies do not differentiate between postdated normally grown infants, large for gestational age, or fetal growth restriction.

Abnormal fetal growth could be a marker for suboptimal intrauterine environment. In a study of 171 children with CP, Blair and Stanley compared the birth-weight distribution expected for a population of the same race, gestational age, sex, maternal height, and parity born in the same geographic region during the same time. Birth weights of children with spastic CP tended to be significantly lower than the median birth weight of the comparison population. Analysis stratified by gestation at delivery suggested that if the reduced birth weight were causally associated with spastic CP, 22% of the cases were attributed to below the 10th percentile of a comparison birth-weight distribution. Poorly grown fetuses between 34 and 37 weeks were at highest risk. The authors concluded that the data indicate that spastic CP is associated with poor intrauterine growth in infants at more than 33 weeks, but identified no important causal mechanism (Am J Obstet Gynecol 1990;162:229).

Term births constitute a majority of all births; however, approximately 50% of all births of children with CP are at term (Nelson KB. N Engl J Med 2003;349:18:1765). In an erudite editorial

in the *New England Journal of Medicine*, Dr. Karin Nelson, long-time student of CP, asked the question, Can we prevent CP? Successes in prevention of CP include immunization, decreased exposure to environmental toxins, and iodine supplementation. We lack interventions based on potential CP causes such as perinatal stroke, intrauterine exposure to infection, multiple pregnancy, and birth asphyxia. She urged that future research that could make CP preventable must take into account hypotheses and animal models that can translate into careful clinical research. Her conclusion is, "Apart from our ability to avoid exposure to a few associated risk factors in a small minority cases, there is little evidence at present that we can avoid cerebral palsy."

In the study abstracted here by Jarvis et al., the risk of CP is linked not only to low-birth-

weight infants, but also to excessively high-birth-weight infants. The CP rate had a reversed J-shape, which is similar to causes of perinatal mortality. Ellenberg and Nelson reported a similar relationship between intrauterine growth and the risk of CP (*Am J Dis Child* 1979;133:1044). The study abstracted here differs because of a much larger database. Brain damage *in utero* might trigger abnormal growth patterns through endocrine or other pathways. This further supports the 80% of CP that has its origin in the antenatal period. How do we detect the antenatal abnormality that leads to CP? That question remains controversial. Once the abnormality is detected, the next major hurdle is what to do. We cannot be caught standing still in our quest on the causes and prevention of CP; however, we do well if we move ahead slowly with clinical studies based on sound data.—RCC)

A National Survey of Residents' Self-Reported Work Hours: Thinking Beyond Specialty

DeWitt C. Baldwin, Jr., Steven R. Daugherty, Ray Tsia, and
Michael J. Scotti, Jr.

Accreditation Council for Graduate Medical Education, Chicago, Illinois; the Department of Psychology, Rush Medical College, Chicago, Illinois; the Department of Pediatrics, Georgetown University Medical Center, Washington, DC; and the American Medical Association, Chicago, Illinois

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ABSTRACT

No other group in the United States work force experience the levels of fatigue and sleep deprivation experienced by residents. Unlike those working in the airline and railroad industries, which also affect public safety, medical residents still average approximately 80 hours a week on duty and many work longer than this. The present national random sample enlisted postgraduate year 1 (PGY1) and year 2 (PGY2) residents in the 1998 to 1999 training year. Completed survey forms were received from 3604 residents, 64% of those contacted. Participants came from many specialties and institutions. The PGY1 residents reported having worked an average of 83 hours per week, and the PGY2 group, 76 hours, a nearly 10% difference. General surgery residents reported nearly twice the work hours per week as did pathology residents in both years. Residents in general spent 75% to 80% of their time in direct patient care. Forty percent of PGY1 residents worked more than 90 hours per week, as did 32% of the PGY2 group. Approximately 16% of PGY2 residents, but many fewer PGY1 residents, reported doing work outside their programs ("moonlighting"). The PGY1 and PGY2 groups reported sleeping an average of 5.8 and 6.0 hours per night, respectively. Men worked longer hours than women, as did residents with children compared with those who were childless. Total work hours correlated

significantly with self-reported stress levels. Residents working 80 hours or more per week were 1.6 times more likely to have experienced a serious accident or injury and were 1.9-fold likelier to have had a serious conflict with a fellow resident. They also reported more conflict with nurses and attending staff. Longer work hours correlated with alcohol use, noticeable weight gain, and the use of medication to stay awake. Those working longer hours also were 1.5 times more likely to report a "significant medical error." In view of the wide range of residency programs and specialty requirements, it is unlikely that any arbitrary limit on work time will be a satisfactory response to residents and patient care concerns. Those applying for a residency program should benefit from comprehensive and reliable information about educational opportunities and work-hour expectations in their specialty of interest.

EDITORIAL COMMENT

(Worldwide, the limiting of work hours for residents is not new; Germany and The Netherlands have recently established maximum work hours from 48 to 56 hours per week, whereas Great Britain and Australia have mandated a 72-hour limit. In the United States, the average resident work hours have decreased over the past 20 years; however, the Accreditation Council of Graduate Medical Education (ACGME) published a regulation about duty hours on July 1, 2003. Henceforth, all ACGME-sponsored programs had to comply with a mandated 80-hour per week average over 4 weeks. To secure data from residents regarding residency work hours, Baldwin et al. performed a national random survey of postgraduate year 1 (PGY1) and 2 (PGY2) residents in the 1998 to 1999 training year using 44 questions and 144 separate data elements related to their residency experience. Completed surveys were received from 3604 of the 5616 (64.2%) residents contacted. PGY1 residents reported working an average of 83 hours a week versus 76.2 hours for PGY2 residents. Total work hours were significantly correlated with resident stress and hours of sleep per week. Residents averaging more than 80 hours per week were more likely to be involved in personal accidents or injury, a serious conflict with other staff members, or significant medical errors. The authors concluded that nearly half of the PGY1 and one third of the PGY2 residents reported working more than 80 hours per week. The authors believe it seems unlikely that an arbitrary limit or a simple decrease in work hours will provide a satisfactory solution to many resident and patient care concerns (*Acad Med* 2003;78:1154).

Apparently, the medical profession is one of the last to limit work hours under the rubric of

public safety. In July 2003, the ACGME mandated for specialty and subspecialty programs that over a 4-week period, residents must be limited to an average of 80 hours a week, be on call every third night, and have 1 day in 7 free from patient care. Also, programs are required to give residents a minimum of 10 hours rest between times on duty. There is a provision that allows for limits regarding on-call duties for 24 hours, plus "an added period up to 6 hours for continuity and transfer of care, education briefing, and didactic activities, during which no new patients may be admitted" (ACGME. Common Program Requirements, Approved February 2003. Available at: <http://www.acgme.org>. Accessed July 30, 2003). Whether the ACGME work program requirements will enhance patient safety is open for continued discussion and analysis. The article abstracted here clearly points out that it is more than hours that make up the workweek. Most importantly, physician wellness and an efficient and supportive work environment must be in place to effect physician wellness and quality patient care. It could very well be that surviving the medical school rigors inflates a physician's ego to a point where, as a resident, he or she might lack clarity of vision and lucidity of thought when it comes to their own wellness. I truly believe that the work hours in and of themselves will not solve the problem. There is much more to personal wellness than limiting work hours.

Each year, as Director of Graduate Medical Education at UNC Hospitals, I exhort all residents not to drive when tired. Yet, this admonition is not well understood until we have motor vehicle accidents involving residents who drive while tired. The effects of sleep deprivation could lead to changes in personal hygiene and

weight, and to greater use of medication to cope with the stress and stressors of residency. I agree with the authors of the article abstracted here that attention needs to be focused on other aspects of the residency experience, including the effects of sleep deprivation and fatigue, and on enhancing the learning environment so that personal needs and goals of the residents are appreciated and obtained. In other words, personal wellness and health during a residency must be equal to that of the learning experience.

In collaboration with Dr. Kathy Andolsek, Associate Director of Graduate Medical Education at Duke Medical Center, we submitted a grant to the Joshiah Macy Jr. Foundation of New York to develop a "model instructional program" on the effects physician fatigue and impairment have on patient safety. The foundation supported the grant. Our goals and objective will be to teach residents and faculty how to recognize, manage, and prevent fatigue, impairment, and burn-out in themselves and their colleagues. It is apparent to us that learners need to take care of themselves first so they can be in the best possible condition to care for others. The physician has many privileges and awesome responsibilities; however, there are other significant stressors that put physicians in harm's way that other professionals and workers do not experience. We believe that adhering to the 80-hour work-week is a beginning, not an end, and that a lot more work needs to be done on personal wellness to understand the adverse effects of a lack of wellness. Education about burnout and impairment should start in medical school; however, these issues might not be taught in medical school or in residency. Our program's curriculum will include workshops, a web site, and CD-ROMs of vignettes, using them as "teachable moments."

In a study to evaluate lifestyle changes that occur during residency, Perry and Osborne selected residents in obstetrics and gynecology, family practice, internal medicine, pediatrics, and surgery to complete a survey related to eating habits, sleep hours, recreation time, exercise, and missing significant events. All specialties noted a significant reduction in the consumption of low-fat meals, sleep hours, exercise, family interactions, and television viewing. Residents noted a significant increase in missed significant events such as birthdays and anniversaries. The authors concluded that residents perceived significant changes in many areas of health and wellness during residency training. Overall, residents in obstetrics and gynecology did not perceive a greater lifestyle alteration compared with other residency training programs (*Am J Obstet Gynecol* 2003;189:679).

Residency is a time for character formation and development. Training programs and institutions should foster not only education in the particular specialty or subspecialty, but develop an environment that is conducive to learning and physician wellness. The future of patient care depends primarily on physician wellness and character development, not wholly on technology. The new ACGME rules, which include not only numeric measures, but also the mandate that we must teach residents the effects of fatigue and sleep deprivation, and develop programs that teach faculty to recognize the effects of resident fatigue, sleep deprivation, or impairment. We should ensure that the future generations of residents have the most outstanding technologic training and advancements in medicine, and should also have an understanding of what it means to manage one's own physical and mental life, as well as that of their families.—RCC)

Preconception Sex Selection for Nonmedical Reasons: A Representative Survey From Germany

E. Dahl, M. Beutel, B. Brosig, and K.-D. Hinsch

Centre for Dermatology and Andrology and Clinic for Psychosomatic Medicine and Psychotherapy, Justus Liebig University, Giessen, Germany

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ABSTRACT

Preconceptual gender selection for other than medical reasons has raised numerous issues, the main one being that such a service, if freely available, will disrupt the natural sex ratio and lead to a severe gender imbalance. This assumes that there will be a definite preference for males or females, and also that there will be considerable demand for sex selection. The advent of MicroSort, a potentially safe and effective flow cytometric method of separating X- and Y-bearing sperm, is expected to widen interest in this practice. Questions concerning preconceptional sex selection were asked of 1094 German individuals 18 to 45 years of age. Fourteen percent of respondents would like to have a boy as their first child, whereas 10% would prefer a girl. Three fourths of those questioned stated no gender preference. Nearly 60% of subjects gave no importance to their children's gender. Another 30% would prefer to have as many girls as boys. When told that sex selection using MicroSort would require them to visit a center, provide a sperm sample, and undergo 3 to 5 cycles of intrauterine insemination with its attendant cost, more than 90% of subjects replied that it was out of the question. Even when told that only 1 cycle would be needed and assured that the procedure would be insured, 94% rejected it. On the assumption that a medication was available to select their children's sex, only 8% would be willing to take it. This survey adds to available evidence that a readily available service enabling gender selection for nonmedical reasons would not be very popular and would not have any substantial social impact. The prospect of a marked gender imbalance from this practice is most unlikely.

EDITORIAL COMMENT

(The ability to determine the sex of a fetus, and more recently the use of preimplantation diagnosis to select the sex of an embryo before transfer to the uterus, has resulted in a thorny ethical problem: sex selection for nonmedical reasons. The present study from Germany addresses an important aspect of this problem: the effect of sex selection on gender balance in the population. Slightly over 1000 randomly selected subjects, aged 18 to 45, were interviewed by telephone and asked 5 questions designed to determine the subjects' preferences, if any, for the selection of a boy or girl if the technology to do that before birth or even before conception was available without risk. Only 5% of the subjects would avail themselves of such technology to predetermine the sex of their child. As far as gender preferences for all children born, 88% of the respondents chose either equal numbers of boys and girls or no preference at

all. The authors' conclusion is that if sex selection technology becomes highly reliable, noninvasive, safe, and affordable, it will have only a negligible societal impact and will not result in a severe gender imbalance. The authors also point out that most clinics offering prenatal or preconception gender selection in the United States and Europe report that over 90% of the couples request the service for family-balancing purposes, and they are as often seeking to have a female child as they are to have a male child. Most are families in which there is more than 1 child of the same sex.

The present study was conducted in Europe. If a similar study were conducted in Asia, the results would undoubtedly have been quite different. Between 2 and 5 million female fetuses are intentionally aborted in India annually (Allahbadia GN. *J Assist Reprod Genet* 2002;19:411). Also, preimplantation gender diagnosis is being

used in India, and probably other countries, for prenatal sex selection (Malpani A, et al. *Hum Reprod* 2002;17:11). In Korea, China, and Taiwan, where there are cultural preferences for sons, the use of prenatal sex selection has produced worrisome gender imbalance (Westley SB. *Asia Pac Pop Policy* 1995;34:1). Many regard the widespread use of prenatal sex selection in these countries as simply 1 more manifestation of the societal discrimination against women of all ages. Official government policies in these countries discourage prenatal sex selection, several Asian countries have laws forbidding it, and professional policies discourage physicians from offering these services. Nevertheless, the laws are not widely enforced and families can readily find physicians to provide the services.

There is ambivalence among professional organizations about the practice of prenatal sex selection for nonmedical reasons. The ethics committee of the American Society for Reproductive Medicine maintains that couples should be free to use sex selection, but providers should encourage couples to allow sex determination to be resolved by chance (*Fertil Steril* 1999;72:595). The official policy of the United Nations is that governments should take necessary measures to prevent prenatal sex selection. The International Federation of Gynecology and Obstetrics and ACOG are opposed to nonmedical prenatal sex selection on the grounds that it manifests and promotes discrimination against women (ACOG. *Ethics in Obstetrics and Gynecology* 2002).

Dr. Thomas Murray, the President of The Hastings Center, draws attention to important ethical considerations about nonmedical prenatal sex selection (*The Worth of a Child*. Berkeley: University of California Press; 1996:126–130). Policies to discourage or deny the use of nonmedical sex selection run counter to the ethical principal of patient autonomy and the concept that genetic counseling should be nondirective. The claim that genetic counseling is to be based on an ethic of value neutrality and nondirective style “provides no defense against the most outrageous requests by prospective parents.” Sex selection is but the tip of the iceberg for genetic counseling. As Murray notes, “An ethic of non-directiveness is wholly unprepared for the coming avalanche of genetic information.”

Murray also raises the question of whether nonmedical sex selection is unethical in a society where, as documented by the study abstracted here, the practice does not result in gender imbalance and where it is used as often to select female children as to select male children. If the society and our profession are generally appalled by the notion of prenatal testing and abortion for sex selection, whatever the proportion of female to male fetuses, then it is necessary to go beyond the concepts of patient autonomy, value neutrality, and nondirective counseling. If it can be established that prenatal sex selection does not otherwise promote discrimination against women, we need to find good moral reasons for opposing its use.—WAB)