Peri-FACTS®

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About the Program

Peri-FACTS® is a self-instructional program designed to assist obstetric healthcare professionals in the acquisition of the knowledge and expertise needed to provide quality care for childbearing women.

This online, enduring material has been developed from the content of the Peri-FACTS Program, presented by the Department of Obstetrics and Gynecology at the University of Rochester School of Medicine and Dentistry in Rochester, NY.

Target Audience

This educational content is intended for obstetric care providers.

Learning Objectives:

After completing the program modules, participants should be able to:

- Identify factors that place the maternal-fetal unit at risk.
- Discuss the clinical assessment and management of common, obstetric complications.
- Identify baseline fetal heart rate, variability, periodic and nonperiodic changes, and contraction patterns; and describe components of fetal heart rate patterns.
- Identify factors affecting fetal heart rate interpretation and appropriate interventions.

Planning Committee and Author/Speaker Declarations:

The ACCME Standards of Commercial Support require that presentations be free of commercial bias and that any information regarding commercial products/services be based on scientific methods generally accepted by the medical community.

The following planning committee members* have disclosed financial interests/arrangements or affiliations with organizations that could be perceived as real or apparent conflict of interest in the context of the subject of their presentation(s). Only the current arrangements/interests are included.

James R. Woods, M.D.	Director declared that no financial interest or relationship exists.
Therese Caffery, R.N.C., M.S.N.P.	Planning Committee Member declared that no financial interest or relationship exists.
Tamara Eis, R.N., M.S.	Planning Committee Member declared that no financial interest or relationship exists.
Kathryn Flynn, R.N.C., M.S.N.P.	Planning Committee Member declared that no financial interest or relationship exists.
Carol Giffi, R.N.C., M.S.N.P.	Planning Committee Member declared that no financial interest or relationship exists.
J. Christopher Glantz, M.D., M.P.H.	Planning Committee Member declared that no financial interest or relationship exists.
Elizabeth Warner, M.D.	Spouse/Partner Consultant to Harter; Secrest; and Emory, LLP
Shirley Warren, R.N., M.S.N.P.-BC	Planning Committee Member declared that no financial interest or relationship exists.

The following author has disclosed financial interests/arrangements or affiliations with organizations that could be perceived as real or apparent conflict of interest in the context of the subject of their presentation(s). Only the current arrangements/interests are included.

Richard K. Miller, Ph.D.	Grant/Research Support from Roche, Johnson and Johnson, Merck, Eastman Kodak, Molecular BioSystems Consultant for Dysmorphologist and Member of Scientific Advisory Board for US Ribavirin Pregnancy Registry; BioGeneriX AG Expert witness for Drugs/Chemicals during pregnancy (Diazepam, Meperidine, Terbutaline, Lead, Isotretinoin)
Susan Roberts, Ph.D., M.P.H.	Consultant for Kendle International, Inc.
Christina Chambers, Ph.D., M.P.H.	Author declared that no financial interest or relationship exists.
Michael F. Greene, M.D.	Author declared that no financial interest or relationship exists.

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For CME content related questions:
University of Rochester Medical Center
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Peri-FACTS®
University of Rochester
Medical Center
Dept. OB/GYN, Box 668
601 Elmwood Avenue
Rochester, NY 14642-8668
Phone: (800) 285-2366
(585) 275-6037
Fax: (585) 276-2080
E-mail:
Peri-FACTS@urmc.rochester.edu
Web site:
http://www.urmc.rochester.edu/obgyn/Peri-FACTS

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Peri-FACTS® #942

May 2011 Topic: Drugs in Pregnancy

Article: Safety of Medications During Pregnancy: The Importance of Prospective Studies, Pregnancy Registries and Healthcare Provider Collaboration

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Peri-FACTS®

An eJournal for Lifelong Learning in Obstetrics

From the University of Rochester's
Department of Obstetrics and Gynecology

This Month, The **Peri-FACTS®** Video Channel presents:

- Examining the Opiate-Exposed Newborn
- Preventing Medication Errors

SAFETY OF MEDICATIONS DURING PREGNANCY: THE IMPORTANCE OF PROSPECTIVE STUDIES, PREGNANCY REGISTRIES, AND HEALTHCARE PROVIDER COLLABORATION

By Richard K. Miller, Ph.D.
Professor, Department of Obstetrics and Gynecology
Environmental Medicine and Pathology/Clinical Laboratory Medicine
University of Rochester Medical Center
Rochester, NY
Susan Sinclair Roberts, Ph.D., M.P.H.
Assistant Professor Clinical Research Program, School of Nursing
University of North Carolina Wilmington
Wilmington, NC
Christina Chambers, Ph.D., M.P.H
Associate Professor of Pediatrics
Family and Preventive Medicine
University of California at San Diego
San Diego, CA
Michael F. Greene, M.D.
Professor of Obstetrics, Gynecology, and Reproductive Biology
Harvard Medical School
Massachusetts General Hospital
Boston, MA

Learning Objectives for **Peri-FACTS®** Case #942: Upon completion, the learner will be able to:

- Define the differences between prospective and retrospective studies and the importance of having a control group/population.
- Identify the critical roles that prospective cohort studies during pregnancy and pregnancy registries play in informed discussions between patients and their healthcare providers concerning the safety of medications during pregnancy.
- Describe three specific ways that healthcare providers and their patients can participate in prospective studies in pregnancy and pregnancy registries.

Peri-FACTS for Antepartum/Postpartum Care Providers

Peri-FACTS' Antepartum/Postpartum program is a variation of the regular Peri-FACTS program. It presents the same monthly learning materials (articles, clinical case studies, and videos) and follows the same program schedule, however, the tests contain only questions that pertain to the corresponding article.
No fetal heart rate monitoring questions are included.

This program has been approved for 1.0 contact hours per clinical case study. Currently, CME credits are not available for this program.

If you have any questions, or would like more information, contact the Peri-FACTS office or visit our website.

Phone: (800) 285-2366/(585) 275-6037 Fax: (585) 276-2080
E-mail: Peri-FACTS@urmc.rochester.edu
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INTRODUCTION

In the approximately six million pregnancies occurring each year in the United States, more than 60% of pregnant women take medications during pregnancy (Andrade, et al., 2004). Pregnant women in the United States take prescription drugs for a variety of reasons:

1. Pre-existing medical conditions, such as asthma or high blood pressure;
2. Conditions that develop during pregnancy, such as gestational diabetes mellitus;
3. To protect the health of the neonate, such as anti-retroviral treatment for women with human immunodeficiency virus (HIV) to reduce mother-to-child transmission; and
4. Acute illnesses, like colds or urinary tract infections.

However, because more than 50% of pregnancies in the United States are unplanned (Finer and Henshaw, 2006), medications may be taken before a woman realizes that she is pregnant (Gyapong, 2003; Yaris, 2004; and Wyszynski, 2009). Inadvertent

exposures inevitably occur, even to medications that expressly are contraindicated during pregnancy, such as isotretinoin and thalidomide (Autret-Leca, 2010, and Bwire, 2011).

Medication exposure during pregnancy can result in adverse pregnancy and neonatal outcomes. Unfortunately, healthcare providers often have inadequate data from which to counsel patients about what medications they should take and which ones they should avoid. Medications typically are approved for marketing by regulatory authorities with little information about the safety of the product used during human pregnancies. A study by Lo and Friedman (2002) indicated that over 80% of new medications approved in the United States have inadequate human pregnancy data to determine teratogenic risk. Regulators must rely on animal data and infrequent reports of pregnancies that inadvertently may have occurred during clinical trials to guide product labeling.

Table 1: Food and Drug Administration Pregnancy Categories

Pregnancy Category A	Controlled studies show no risk to pregnancy: Adequate, well-controlled studies in pregnant women failed to demonstrate risk to the fetus.
Pregnancy Category B	No evidence of risk in humans: Applies if animal studies show increased risk but human studies do not, or, if adequate human studies have not been conducted, but animal findings are negative.
Pregnancy Category C	Risk cannot be ruled out: Human studies are lacking in availability of data, and animal studies are either positive for fetal risk or lacking. In some situations, potential benefits may justify the potential risk.
Pregnancy Category D	Positive evidence of risk: Investigational or postmarketing data show risk to the fetus. In some situations, potential benefits may outweigh the potential risk.
Pregnancy Category X	Drug is contraindicated in pregnancy: Studies in animals or humans, or investigational or postmarketing reports, have shown fetal risk, which outweighs any possible benefit to the patient.

Adapted from 21CRF201.57

In the United States, at the time of approval, medications are assigned a Food and Drug Administration (FDA) Pregnancy Category (see Table 1) (21CRF201.57). The current system was adopted in 1979 and uses five categories: A, B, C, D, and X. The FDA has acknowledged that these categories may mislead healthcare providers to believe that risk is progressive from category A to B to C to D to X. In fact, Categories C, D, and X

weigh both benefit against risk and the quantity and quality of the relevant data, and are not progressively riskier (FDA, 2009). Thus, drugs in categories C or D may pose risks similar to a drug in Category X, and even Category X may not mean the drug is a known teratogen. Another limitation to the current system is that the pregnancy categories do not always distinguish between risks based on human-versus-animal data or between differences in frequency, severity, type of developmental toxicities, and risks that are limited to specific gestational windows of exposure (FDA, 2009). The FDA has proposed major revisions to product labels that address the use of medications during pregnancy and breastfeeding. The proposed labels would include the potential benefits and risks for the mother and the fetus, and how these risks may change during the course of pregnancy (73 Fed. Reg. No. 104 (29 May 2008); FDA, 2009).

PREGNANCY EXPOSURE REGISTRIES

Pregnancy exposure registries are valuable tools for assessing the safety of human pregnancy exposures for many approved medications. The registries frequently are post-marketing commitments to monitor the safety of medications during pregnancy and, thus, often are sponsored by biopharmaceutical companies.

Pregnancy registries typically are designed and implemented in accordance with FDA guidance (FDA, 2002). The registries are subject to oversight from the FDA and require submission of interim and final reports to the FDA at pre-specified intervals.

Most registries include an independent scientific advisory committee to ensure scientific integrity and appropriate patient protection. This committee usually is composed of individuals with expertise in obstetrics, embryology, teratology, pharmacology, epidemiology, pediatrics, clinical genetics, and any relevant therapeutic areas (FDA, 2002). The committee's role is to advise and participate in establishing and operating the registry, review registry progress, participate in raising awareness of the registry, review data at regular intervals for signals of teratogenicity or other safety concerns, classify birth defects, and disseminate information to ensure that results are interpreted and reported accurately (FDA, 2002).

The primary objective of most pregnancy exposure registries is to monitor exposed women for *major developmental effects/defects* associated with pregnancy exposures (FDA, 2002 and Kennedy, 2004). Pregnancy registries are conducted as prospective observational studies that actively collect information on product exposure during pregnancy and associated pregnancy outcomes (FDA, 2002). A prospectively enrolled pregnant woman is one who is enrolled early in pregnancy, before the outcome of pregnancy is known. At a minimum, follow-up lasts until pregnancy ends with a live birth or other birth outcome. If the outcome is a live birth, the infant may be followed for a period of months to years, depending on the suspected potential toxicities and registry objectives. The prospective nature of the pregnancy registry is a major strength of the design in that it reduces bias (FDA, 2002).

Most pregnancy registries are open to anyone in the target population who meets the entry criteria. Patients and healthcare providers provide data to the Registry Coordinating Center at various intervals during pregnancy; data may be provided electronically, on paper, or by phone. The Registry Coordinating Center often functions as a call center to serve as a resource, assist in data collection, facilitate submission of data, and track outstanding data forms and queries.

Accrual of patients in pregnancy exposure registries can be difficult. Often, potential reporters of registry data are unaware of the existence of the registry or the processes by which patients are enrolled. To participate in a pregnancy registry, patients or healthcare providers can contact the registry and request instructions for participation. A comprehensive list of 44 pregnancy registries is posted on the website of the FDA (www.fda.gov) (FDA, 2010). The FDA encourages registry sponsors to post a registry description and contact information on this website to raise awareness of the study and facilitate enrollment.

PROSPECTIVE COHORT STUDIES

In addition to pregnancy registries, prospective cohort studies commonly are used to learn more about the safety of a medication in pregnancy.

Controlled prospective cohort studies are observation studies designed to evaluate the risk or safety of a specific maternal medication or vaccine exposure with respect to a range of adverse pregnancy outcomes, including congenital anomalies, fetal growth abnormalities, spontaneous abortion or stillbirth, preterm delivery, and other maternal or neonatal complications. Because they are prospective in design, pregnant women are recruited into the study before the outcome of pregnancy is known, including prenatal diagnosis of a congenital malformation. This prospective orientation reduces the potential for recall bias that may be inherent in some case-control studies, where women are asked about pregnancy exposures to medications after delivery when their ability to recall exposure may be influenced by the pregnancy outcome.

Controlled, prospective, cohort studies also have the advantage of an internal comparison or control group, i.e., a group of pregnant women who have not had the medication exposure of interest. It is critically important to have an appropriate comparison group because women who are prescribed or who take a certain medication may differ from women in the general population in characteristics that also influence their risk for adverse pregnancy outcomes. For example, women who take a medication for hypercholesterolemia or diabetes may be significantly more likely to be obese than women in the general population, a characteristic that independently poses an increased risk for certain congenital malformations. A controlled prospective cohort study with a comparison group of unexposed women, for whom maternal body mass index data is collected, allows for adjustment for obesity as a potential confounder or effect modifier, and may help to more accurately and validly identify or rule out risks that are due to the medication itself. Similarly, the underlying maternal disease, such as severe asthma, for example, may itself contribute to risks for adverse pregnancy

outcomes. Therefore, a comparison group of pregnant women who have the same underlying disease as the exposed group, but have not taken the medication of interest, can help sort out the potential risks associated with the drug.

Prospective cohort studies also have the advantage of being able to identify or rule out risks for a range of adverse outcomes. This is important because known human teratogens frequently are linked to a pattern of several adverse outcomes. The ability to examine several outcomes may not be possible in case-control studies, because in case-control studies, presence or absence of a single outcome usually is the inclusion criterion. Finally, prospective cohort studies are designed to enable the collection of outcome information for many years after birth. This long-term follow-up allows for the evaluation of neurodevelopmental endpoints to help identify or rule out behavioral teratogens. There are many other types of studies (e.g., randomized controlled trials, retrospective cohorts, etc.), which either are not applicable to studying medications in pregnancy, or are used infrequently.

In the post-marketing arena, many of the controlled prospective cohort studies are conducted by Teratology Information Services (TIS) in the United States and Canada, the European Network of Teratology Information Services (ENTIS), or by collaborations among TIS in various parts of the world. The following two examples illustrate some of the differences and similarities between these various prospective cohort study designs: the Motherisk Multicentre Study of the Safety of the Anti-asthma Medication, Montelukast, and the Organization of Teratology Information Specialists (OTIS) Autoimmune Diseases in Pregnancy Study.

Commonly, TIS studies involve a cadre of healthcare providers and pregnant women who contact a TIS organization during pregnancy seeking counseling regarding the safety of a medication to which the women have been exposed. For selected target exposures, exposed and unexposed comparison women are enrolled in a cohort study, and pregnancy exposure details and follow-up of pregnancy outcomes are obtained via maternal telephone interviews, medical records review, and in some cases, specialized physical examinations of infants.

The Motherisk Montelukast Study identified 180 pregnant women with exposure to montelukast who had contacted, during an ongoing pregnancy, one of six TIS organizations throughout the world (Sarkar, et al. 2009). The 180 exposed women were compared to 180 disease-matched asthmatic women who also had contacted one of the six TIS organizations during pregnancy but who had not taken montelukast, and a second comparison group of women who had contacted one of the six TIS organizations during pregnancy and neither had asthma nor had taken montelukast. Women in the exposed group and both comparison groups were contacted within approximately one year postpartum to collect medical and pregnancy history, other medication use, and birth outcomes. Verification of maternal report was requested from the infants' physicians. No significant differences were found between the three groups in the proportions of infants born with major birth defects. However, significant differences across the three groups were noted for mean gestational age and mean birth weight. The exposed and disease-matched groups were similar, suggesting that

maternal asthma and not the specific medication under study was responsible for these differences. The findings of this study provided a level of reassurance to clinicians and patients who have taken montelukast during pregnancy.

The OTIS Autoimmune Diseases in Pregnancy Study is an ongoing collection of disease-based cohort studies with a special focus on several medications used to treat rheumatoid arthritis, psoriasis, Crohn's disease, and ankylosing spondylitis. One of the target medications, leflunomide, is a Category X medication contraindicated in pregnancy due to concerns over teratogenicity in animal species and the drug's mechanism of action. Using a prospective cohort design, 64 women who had taken at least one dose of leflunomide for rheumatoid arthritis during pregnancy were enrolled and compared to 108 women with rheumatoid arthritis who had not taken leflunomide and 78 women who had neither the disease nor had taken the drug (Chambers, 2010). Exposure, medical history, pregnancy history, demographic factors, and measures of disease severity for the rheumatic groups were collected via maternal telephone interviews at three standard time points during pregnancy. Outcome data were collected via maternal interview and medical records review with standard follow-up to one year of age. In addition, approximately 90% of all live-born infants received a specialized and blinded physical examination by one of a team of study dysmorphologists/geneticists to evaluate both major and minor birth defects. There were no significant differences in the proportion of infants with major birth defects, and no specific pattern of minor malformations was identified in the exposed infants. Initially, there appeared to be differences between the three groups in gestational age at delivery and birth weight, but after adjustment for confounders, there were no significant differences between the leflunomide-exposed pregnancies and the disease-matched comparison group. The findings of this study, although based on small numbers, provided the first human study data and some reassurance for clinicians and their patients who inadvertently are exposed to leflunomide in early pregnancy.

The primary limitation of many TIS-based, prospective, cohort studies relates to sample size; typically these studies involve fewer than 200 exposed women. Also, TIS studies rely heavily on motivated callers to the TIS for recruitment of participants, which may result in bias. To address these issues, collaborative and more comprehensive efforts to increase referrals of a broad representation of both exposed and comparison women are underway. These efforts rely on healthcare providers and patients who are aware of ongoing cohort studies, and who are willing and committed to contribute their time to gain better information regarding medication exposures during pregnancy.

HEALTHCARE PROVIDER COLLABORATION

The healthcare provider (HCP) plays a central role in furthering knowledge about medication effects in pregnancy. In many cases, we have relied on the astute clinician to make the connection between a number of cases of patients with a specific problem and their common prenatal exposure, e.g., Arthur Herbst, who first noted the link between in-utero exposure to diethylstilbestrol (DES) and clear cell adenocarcinoma in females (Herbst, 1970). However, rather than relying on the serendipitous chance that

a clinician could and would be able to notice less striking teratogenic associations, we are all provided with the opportunity to study these issues prospectively by participating in pregnancy registries. This means the pediatrician, the oncologist, the pathologist, every patient, and HCP.

The challenge is to engage every nurse, medical student, resident, physician assistant, nurse practitioner, midwife, pharmacist, psychiatrist, family medicine physician, internist, and obstetrician/gynecologist in identifying pregnant women or those planning pregnancies and at risk due to the medications being prescribed. Then they need to reach out to the appropriate pregnancy registries to provide the individual patients that will establish the risk for our essential medications and treatments for disease.

Imagine seeing your next patient on a selective serotonin reuptake inhibitor or taking an agent that you are concerned might be a teratogen, e.g., ribavirin. With sufficient information from a pregnancy registry, you might be able to reassure them about the risks. Some information is available but usually with insufficient numbers of patients.

You will find many exposure information sheets for your patients at www.otispregnancy.org; however, many of those information sheets could be improved by having many more prospective studies. In many instances, your patient may not be taking the drug but may have the disease. Your patient could be an outstanding control subject for the study. You are the critical link to advise your patient of the importance of this effort. Without you and your patient, new knowledge will not exist.

Recommendations for your healthcare team:

1. Evaluate each pregnant patient as if you are answering these risk questions for yourself.
2. Keep the list of pregnancy studies near your phone (Appendix A) and patient charts.
3. Even if your patient discontinues the medication, consider asking her to participate in these critical national studies for the sake of all mothers and children.
4. Assist the patient in contacting the registry, while in your office.
5. Follow up when asked about outcome of the pregnancy and the health of the mother and baby.
6. If you have questions about whether there is a study for a drug of concern or disease condition, call (866) 626-6847 (OTIS PREGNANCY RISK LINE). They will direct you to a pregnancy registry.
7. If you need information about drug usage during pregnancy or have concerns about environmental exposure during pregnancy, call (866) 626-6847 (OTIS PREGNANCY RISK LINE). They can help.

SUMMARY

Prospective cohort studies and pregnancy exposure registries are valuable tools for accruing information on medication safety in pregnancy. These studies play an important role in informing discussions between patients and their healthcare providers concerning the safety of medications during pregnancy. Participating in these studies is an available option for patients who meet the eligibility criteria and their healthcare providers. Obstetric healthcare providers can expedite the collection of information on the safety of medications in pregnancy by reporting exposed pregnancies early and providing follow-up data as requested, in accordance with the registry's protocol. Obstetric healthcare providers also can assist by informing their patients of existing studies and encouraging them to participate.

Up-to-date information on active pregnancy registries and prospective cohort studies can be found on the websites of the:

- Organization for Teratology Information Specialists (www.otispregnancy.org)
- Food and Drug Administration (http://www.fda.gov/ScienceResearch/SpecialTopics/WomensHealthResearch/ucm134848.htm)

Appendix A contains an abbreviated table of pregnancy studies as listed on the FDA website. This table is designed to be photocopied and kept in your pocket or on your desk. Please use it as your reference guide.

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Appendix A. Abbreviated List of Pregnancy Studies - Adapted from the FDA's Website (FDA, 2010)

Pregnancy Studies for Specific Medical Conditions

Medical Condition	Telephone Contact Information
Autoimmune Diseases	877-311-8972
Cancer	877-635-4499
Epilepsy	888-233-2334
HIV/AIDS	800-258-4263
Transplants Anti-rejection Medicines	215-955-4820

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Pregnancy Studies for Specific Medical Products

Product Name	ContactInformation
Gardasil Vaccine	800-986-8999
Hepatitis B Vaccine, Twinrix, Engerix-B, Recombivax H, Comvax	800-670-6126
Fabrazyme® (agalsidase beta)	617-591-5500
Enbrel (etanercept)	877-311-8972
Betaseron	800-478-7049
Avonex (interferon beta-1a)	800-811-0104
Arava (leflunomide)	877-311-8972
Amevive (alefacept)	866-834-7223
Amerge (naratriptan) Imitrex (sumatriptan)	800-336-2176
Aldurazyme® (laronidase)	617-591-5500,
Humira (adalimumab)	877-311-8972
Janumet (sitagliptin phosphate plus metformin HCl)	800-986-8999
Januvia (sitagliptin phosphate)	800-986-8999
Exenatide	800-633-9081
Keppra (levetiracetam)	888-537-7734
Lamisil	800-670-6126
Maxalt (rizatriptan)	800-986-8999
Meridia	800-670-6126
Myozyme®(alglucosidase alfa)	617-591-5500,
Naglazyme	http://clinicaltrials.gov/ct/show/NCT00214773?order=2
Neoral (cyclosporine, USP) Modified	888-522-5581
Orencia (abatacept)	877-311-8972
Raptiva (efalizumab)	877-727-8482)
Rebif (interferon beta-1a)	877-447-3243
Ribavirin	(800)593-2214
Singulair (montelukast)	800-986-8999
Singulair (montelukast)	800-670-6126

Product Name	ContactInformation
Twinrix	888-825-5249
Tysabri	866-831-2358
Varivax, Zostavax, Proquad	800-986-8999
Wellbutrin, Wellbutrin SR, Zyban(bupropion)	800-336-2176
Xolair	866-496-5247
Cymbalta ®(duloxetine HCl)	866-814-6975
Nplate®(romiplostim)	877-675-2831
Herceptin® (Trastuzumab)	800-690-6720
Provigil® (modafinil)	866-404-4106
Nuvigil® (armodafinil)	866-404-4106
Savella	877-643-3010

For clarifications and possible new studies,
do not hesitate to contact (866) 626 6847
(the OTIS Pregnancy Line).

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The Division of Maternal-Fetal Medicine and Perinatal Nursing, Department of Obstetrics and Gynecology,
University of Rochester, Strong Memorial Hospital, Rochester, NY

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