Ethical Challenges of Pregnancy Prevention Programs

Robert Bonebrake, MD; Murray J. Casey, MD; Christopher Huerter, MD; Binh Ngo, MD; Richard O'Brien, MD; Marc Rendell, MD

Certain useful pharmaceutical agents carry a high risk of embryopathy. The US Food and Drug Administration (FDA), in cooperation with drug manufacturers, has established pregnancy prevention programs (PPPs) to reduce the incidence of birth defects for thalidomide (STEPS® [System for Thalidomide Education and Prescribing Safety]) and isotretinoin (iPLEDGE™) but not for other teratogenic drugs in clinical use. These programs are complex and raise important concerns regarding privacy, the clinician-patient relationship, and convenience of medical care. Furthermore, pregnancies continued to occur in isotretinoin-exposed females during the first full year of the iPLEDGE program. We review the design and application of STEPS and iPLEDGE and consider the ethical issues raised by the introduction of these programs. The goal is to eliminate birth defects caused by teratogenic agents, without making procedures so onerous that they result in restricted access to useful agents. Confidentiality must be maintained, and the rights of disadvantaged populations and individuals with special religious concerns must be protected. Informed consent must be complete and include all risks of treatment, including risks of contraceptive methods. All teratogenic agents should be covered by PPPs, which then must be no more burdensome than requirements that have existed for many years for other controlled substances.

Cutis. 2008;81:494-500.

Accepted for publication September 24, 2007.

Drs. Bonebrake and Casey are from the Department of Obstetrics and Gynecology, Dr. Huerter is from the Department of Dermatology, Dr. O'Brien is from the Center for Health Policy Ethics, and Dr. Rendell is from the Department of Medicine, all at Creighton University School of Medicine, Omaha, Nebraska. Dr. Ngo is from the Division of Dermatology, Harbor–University of California at Los Angeles Medical Center, Torrance.

The authors report no conflict of interest.

Correspondence: Marc Rendell, MD, Department of Medicine, Creighton University School of Medicine, Suite 6715, 601 N 30th St, Omaha, NE 68131 (rendell@asndi.com).

Pregnancy Prevention Programs

There are many pharmaceutical agents with documented teratogenic effects. The US Food and Drug Administration (FDA) has established categories of reproductive risk. Pregnancy category D indicates positive evidence of human fetal risk, but potential benefits may warrant use of the drug in pregnant females despite potential risks. Pregnancy category X is reserved for agents with risks of use in pregnant females that clearly outweigh the benefits.[1] Despite warnings, unplanned pregnancies do occur in females using agents classified as pregnancy category D or X. The FDA developed 2 programs to control the distribution of thalidomide and isotretinoin, both with perceived high reproductive risks.[2,3]

Thalidomide—Historically, the most notorious teratogenic agent is thalidomide, which was originally marketed as a sedative in West Germany and the United Kingdom in the late 1950s. In 1961, Lenz and Knapp[4] and Lenz[5] in Germany and McBride[6] in Australia implicated thalidomide use in pregnancy as the cause of a sudden epidemic of devastating congenital malformations, including phocomelia, a form of limb aplasia.[7] Thalidomide was withdrawn from the market. However, in 1965, Sheskin[8] discovered that it was effective in treating erythema nodosum leprosum, a severe and distressing complication of leprosy, and in the late 1990s, reports suggested the effectiveness of thalidomide in multiple myeloma.[9,10] Further studies led to eventual FDA approval of thalidomide for the treatment of erythema nodosum leprosum and multiple myeloma.[11] Additional studies have promoted thalidomide as an adjunct in several solid cancers[12-14] and a number of refractory skin conditions.[15,16]

With reentry into the market, the FDA and manufacturer of thalidomide introduced STEPS® (System for Thalidomide Education and Prescribing Safety), a pregnancy prevention program, to limit the possibility of birth defects.[17] At the first visit with a prescriber, the use of thalidomide versus

alternative therapies is discussed and patients are counseled and given educational materials on the risk of birth defects and other side effects, including the high incidence of neuropathy and phlebothrombosis. Females of childbearing potential must use 2 forms of contraception at the same time, including at least one highly effective method (primary) and one physical barrier method (secondary)(Table), initiated at least 4 weeks before beginning therapy, during therapy, and for at least 4 weeks following discontinuation of thalidomide. Females do have the right to abstain from sexual intercourse with males as an alternative to contraception. A consent form must be completed and signed, and a mandatory and confidential survey enrollment form must be completed by patients. A quiz is administered to patients (monthly for females of childbearing potential and every 6 months for females not of childbearing potential) and physicians via interactive voice response system to assess patient understanding of program requirements. Prior to providing a thalidomide prescription to females of childbearing potential, a negative pregnancy test must be obtained within 24 hours prior to initiating therapy, even for females who are abstinent. The prescription must be filled within 7 days. The pregnancy test must be repeated weekly for the first 4 weeks and every 4 weeks (28 days) thereafter in order to continue receiving monthly prescriptions. If pregnancy does occur during treatment, the drug is immediately discontinued and a report is issued to the FDA and the manufacturer.

Males also must participate in the STEPS program because of possible transmission of thalidomide in semen. Males are instructed to use a latex condom each time they have sexual intercourse with females, even if they have undergone successful vasectomy. They must complete the survey form every 3 months, but prescriptions are still issued every 4 weeks.

Approximately 124,000 patients (43% female) were registered with the STEPS program between September 1998 and December 31, 2004.[17] Multiple myeloma and other cancers are largely diseases of late adulthood; therefore, only 6000 patients in the STEPS program were females of childbearing potential, representing approximately 5% of all patients and 11% of all female patients. Seventy-two females of childbearing potential had positive pregnancy test results; 69 were false-positive results. Of the remaining 3 patients, 1 became pregnant while taking thalidomide and 2 were determined to be pregnant before they received thalidomide.[17]

Isotretinoin—Because of the relative infrequency of thalidomide use in females of childbearing potential, the STEPS program has not been viewed as a barrier to access to this agent. However, the dilemma posed by isotretinoin is much more difficult. Retinoic acid derivatives frequently are used as topical agents to treat acne, a disease primarily affecting adolescents in whom the risk of unplanned pregnancy is high. In aggressive cases of cystic nodular acne with the possibility of disfiguring scar formation, oral isotretinoin is considered the most effective therapeutic agent,[18,19] but it is highly teratogenic. Embryopathy associated with the mother's exposure to this agent during the first trimester of pregnancy includes craniofacial, cardiac, thymic, and central nervous system malformations.[20] With the initial release of isotretinoin as a

Birth Control Methods

Highly Effective Methods (Primary)
Copper-bearing IUD
Daily oral hormonal contraceptive agents
Depot medroxyprogesterone acetate injection
Long-term implantable hormonal contraceptive agents
Progesterone-releasing IUD
Transdermal hormonal contraceptive patch
Tubal ligation
Vaginal hormonal contraceptive ring
Vasectomy
Physical Barrier Methods (Secondary)
Cervical cap
Diaphragm
Female condom
Male condom
Vaginal sponge
Methods Based on Limitation of Sexual Intercourse
Abstinence
Natural birth control methods

Abbreviation: IUD, intrauterine device.

pregnancy category X drug in 1982, patients were given a brochure describing the agent's risks, with warnings to avoid pregnancy. The first report of a pregnancy with malformations in 1983 prompted 2 so-called Dear Doctor letters and the distribution of red stickers to pharmacies with further warnings. Continued pregnancies with malformations resulted in 7 Dear Doctor letters between 1984 and 1988 and an FDA advisory committee was convened.[21,22] In response to the FDA recommendations, the manufacturer began a pregnancy prevention program (PPP) that included educational materials for clinicians, a boxed warning, and patient reimbursement for contraceptive counseling. The drug was dispensed in a blister pack with an avoid pregnancy symbol.

Despite these measures, isotretinoin-exposed pregnancies occurred.[23,24] The manufacturer documented 1995 isotretinoin-exposed pregnancies from 1982 to 2000. Of these pregnancies, 1214 were terminated electively, 213 were spontaneous abortions, and 19 were missed abortions. In all, 383 live births occurred; 162 newborns had congenital anomalies. It was concluded that compliance with the PPP was unsatisfactory, which led to an agreement on August 12, 2005, between the FDA and the manufacturers of systemic isotretinoin to create an enhanced PPP similar to STEPS. iPLEDGE™ requires mandatory computerized registration of prescribers, patients, pharmacies, and wholesalers. As in the STEPS program, an informed consent form must be signed by patients. Birth control is required for all female patients with menses including females who have had tubal ligation as well as females in the premenstrual stage, with pregnancy tests required one month prior to, during, and one month after isotretinoin treatment. Women who have documented menopause or surgical sterility, defined as hysterectomy or bilateral oophorectomy, and females who agree to forego sexual intercourse with males are not required to have contraception. For each isotretinoin prescription, the iPLEDGE computer program grants authorization to the pharmacy to dispense the product only if all the criteria for the prescriber, patient, and pharmacy have been met. Identification codes are used to protect patient privacy.[23,24]

Each month, females of childbearing potential must have a pregnancy test and access the iPLEDGE system to document the 2 forms of birth control that she is using prior to receipt of a prescription. Seven days are allotted to access the system and fill the prescription. If a pregnancy test is not performed or more than 7 days elapse from the time of the prescription, the system does not allow dispensation of medication.

Ethical Concerns

It is important to consider the ethical issues raised by the STEPS and iPLEDGE programs. The birth of children with impairments is an emotionally painful event for parents, often resulting in lifelong burdens for the family as well as society. Therefore, there is an obligation to prevent births in female patients exposed to teratogenic agents. Conversely, the compulsory aspects of these programs raise important questions. Carriers of genes for Tay-Sachs disease, sickle cell anemia, cystic fibrosis, and Huntington disease are not subject to governmental regulation of reproductive behavior. Furthermore, there is no regulation of reproduction of females who abuse either ethanol or cigarettes, despite demonstrated harm to the fetus.[25] Other pregnancy category X medications often are dispensed to pregnant females,[26] but none of these medications, aside from thalidomide and isotretinoin, are regulated. In particular, HMG-CoA reductase inhibitors and methotrexate are not covered by a PPP; surprisingly, oral acitretin, which also is a pregnancy category X retinoic acid derivative that is used for long-term treatment of psoriasis, is unregulated.[27] Many practitioners are prescribing acitretin for acne to circumvent the cumbersome iPLEDGE procedures.

There have been abundant criticisms of the iPLEDGE program, suggesting there was insufficient consideration of the views of patients and clinicians prior to its design and implementation.[26,27] It is not our intent to assess the validity of these criticisms but rather to evaluate the obstacles to the optimal ethical implementation of these programs. It is important to recognize that the simplest solution to avoiding birth defects due to teratogenic drugs is to ban their use, as was initially done with thalidomide. However, a ban on an effective drug without existing alternatives could cause harm not only to females of childbearing potential but also to males and females not capable of bearing children, which might have been avoided with these treatments.

The iPLEDGE program has been criticized by practicing dermatologists because of the cumbersome nature of the measures introduced.[28,29] Any failure in the process or exception to the 7-day window of time results in refusal to dispense drug. A vacation, change of prescriber, or computer data entry error will stop the process, requiring time-consuming calls to the iPLEDGE center. The cost of implementing the relatively onerous procedures also is a negative factor, particularly in relatively resource-poor inner city hospital centers. In these busy hospital clinics, the burden of compliance with rigid appointment times may prove too great for patients and staff, particularly in disadvantaged populations in which

compliance is already an issue. The current program requires not only literacy but also the ability to perform the required survey procedures.

Inconvenience is not an ethical issue unless it is so problematic it constitutes a barrier to access to the drug.[3,30] The highly centralized programs introduced by STEPS and iPLEDGE interrupt the usual relationships between prescribers, patients, and pharmacists. There are financial disincentives for independent practitioners to prescribe isotretinoin because there is no reimbursement for the time required to carry out the procedures. It would be unfortunate if the main reason for reduced exposure to isotretinoin in pregnant females was simply decreased overall use of this drug.

An additional potential barrier to access relates to the willingness of individuals to share their personal information. The iPLEDGE program requires female patients to register and document their use of birth control methods at several levels (ie, the clinician's office, the pharmacy, the iPLEDGE database), which constitutes a substantial privacy risk. With 85% to 90% of overall use of isotretinoin in females aged 15 to 44 years, many unmarried female patients are required to share information regarding their sexual activity, including females younger than 18 years who engage in sexual relationships without parental approval. It has been suggested that imposition of parental consent on the decision to use contraceptive treatment reduces the willingness of these patients to obtain these agents[31,32] and, in our society, parental consent rarely is not required, despite attempts at legislation.[31-33] However, the iPLEDGE program requires use of contraception and isotretinoin cannot be used by patients younger than 18 years without parental consent.

There can be no conception without sexual intercourse, so abstinence will avoid pregnancy, but it is not considered reliable by the iPLEDGE program for previously sexually active females. There are several legal cases wherein females who clearly understood the risks of isotretinoin were unsuccessful in maintaining abstinence and delivered children with birth defects.[34-36] The literature distributed by the PPPs discourages natural means of birth control, but contraception is not accepted by the Catholic church and there are non-Catholic females with similar religious beliefs. Furthermore, the use of contraception is only as effective as the motivation to use the method. In a study among a nationally representative sample of 10,683 women receiving abortion services in 2000 to 2001, inconsistent use of contraception was the main cause of pregnancy. Pregnancy occurred in 13% to 14% of females who actually claimed good compliance with contraception (ie, condoms, oral contraceptives).[37] Moreover, the perception and use of contraceptives varies widely among different ethnic and socioeconomic groups. In socioeconomically deprived groups, there may be a lack of trust in the medical care system, which impairs the decision to use contraceptives.[38-41] In a study of more than 300 African American women, 67% reported perceptions of discrimination when attempting to obtain family planning services.[41]

Females who have intermittent spontaneous sexual intercourse constitute the greatest risk of unplanned pregnancy. Thus, there is considerable pressure to prescribe daily hormonal contraceptive methods, despite certain unavoidable risks, for females who are to receive isotretinoin therapy. The principal risk in young females (adolescents to women in their early 30s) affected by iPLEDGE is venous thromboembolism, with an incidence exceeding 1 per 1000. This incidence increases 10-fold with the use of oral contraceptives.[42-44] Furthermore, this risk is substantially greater in patients with thrombophilic conditions such as deficiencies of antithrombin and proteins C or S, elevated levels of factors VIII:C or V Leiden, and prothrombin G20210A.[45,46] Venous thromboembolism can lead to fatality when complicated by pulmonary embolism or cerebrovascular thrombosis. In a Swedish study, the overall refined mortality rate due to venous thromboembolism in females using combined oral contraceptives was 7.5 (CI, 4.7–10.3) per million user-years, with rates increasing with age. In the age group of 15 to 24 years, the mortality rate was 6.0 (CI, 3.1–10.5) per million user-years in females using combined oral contraceptives as compared to 0.3 (CI, 0.0–1.2) per million woman-years in females using combined oral contraceptives.[47]

Informed Consent—The issue of informed consent is at the center of the challenges posed by the STEPS and iPLEDGE programs. In many ways, these programs are patterned after clinical research procedures for investigational drugs, with a protocol, informed consent, and collection of information. However, the consent process in these programs has a less comprehensive description of possible hazards, risk, and discomforts of participation than most research studies. For example, there is no clear description of the risks of the various forms of contraception. Moreover, the current consent process is unbalanced in its emphasis on birth defects; similar attention is not given to other risks such as the high frequency of painful neuropathy and increased risk of thromboembolism associated with thalidomide,[48,49] as well as the side effects of isotretinoin, including depression, pseudotumor cerebri,

gastrointestinal tract damage, myalgia, arthralgia, osteoporosis, hearing problems, night blindness, and severe hypertriglyceridemia. Although the information is provided to patients and prescribers for both agents, there is no substantial warning against using the drugs in patients with a history of psychiatric disorders or thromboembolism, or other susceptibilities to these adverse events. Explicit inclusion and exclusion criteria for participation in the programs are not present.

Other informed consent deficiencies include the lack of an explicit statement concerning the right to withdraw from treatment and failure to explain options to the patient in the event of a research-related injury. The most serious consent issue is the absence of review and recourse for the patient. It is difficult to understand how these programs could have been created without an independent central review board to provide surveillance and protect the rights of patients who participate.

Equal Treatment—Another perceptual complaint is the lack of equal treatment of males and females. To the credit of both programs, males are obligated to consent and participate, albeit with fewer requirements. Naturally, males do not have to undergo pregnancy tests.

Long-term Effectiveness—The most serious ethical concern related to PPPs is the absence of a protocol to assess their long-term effectiveness. According to data released by isotretinoin manufacturers and reported to the FDA on August 1, 2007, a total of 137,415 females of childbearing potential registered with iPLEDGE in 2006. Of these patients, 91,894 received at least 1 isotretinoin prescription; 78 became pregnant while taking the drug, 8 became pregnant within 1 month after they stopped taking the drug, and 10 were already pregnant before taking it including 2 who had pregnancy tests falsified.[50] These statistics suggest that the strict and intrusive regulations of iPLEDGE have not had the desired effects.

Comment

The STEPS and iPLEDGE programs were created in response to a profound ethical dilemma—the need for medications that had unique effectiveness but also had known embryopathic effects. In both cases, complex and cumbersome programs of strict overview of reproductive behavior of female patients have been developed, requiring substantial intrusion into personal privacy and the relationship between prescribers and their patients.

In defense of the FDA and the manufacturers of the 2 products, their 20-year experience with isotretinoin showed that vigorous pursuit of voluntary pregnancy prevention via education of patients and clinicians failed to eliminate the birth of children with deformities. Still, the centralized measures imposed by the FDA have not achieved strong support among prescribers or pharmacists and have raised a number of ethical concerns that cannot be easily dismissed. Furthermore, there has been no major reduction in exposure of pregnant females to isotretinoin. It is not our purpose to criticize the well-intentioned and well–thought-out effort to deal with a difficult and emotionally painful problem; instead, we hope to stimulate a reexamination of the approach that will lead to a plan that may be applied not only to the prescription of thalidomide and isotretinoin but also to embryopathic agents in general. Undoubtedly, the key elements of such a plan would be to provide comprehensive information to patients so they can make individual choices, protect personal privacy, safeguard the rights of females to choose abstinence for birth control, and reduce the intrusion of regulation into the relationship of prescribers and their patients.

Our primary suggestion is that regulation of these 2 products should not be unduly onerous. The distribution of all prescription drugs is regulated, and current cost concerns lead to considerable restriction of dispensation, particularly of brand-name drugs. Furthermore, the dispensation of narcotics has been highly regulated for more than 80 years and has raised less objections than the current PPPs. No drugs are as highly regulated as those carrying investigational status, yet the dispensation of agents in clinical research settings appears to be more flexible and grants more individual freedom than the STEPS and iPLEDGE programs.

We call on the manufacturers, the FDA, prescribing clinicians, and pharmacists to join in the reconsideration of the current approach to the dispensation of teratogenic agents. We believe that there can be improvement in the PPPs, strengthening their ethical foundations, eliminating impediments to drug access, and permitting greater applicability to the elimination of drug-induced birth defects.

REFERENCES

1. Addis A, Sharabi S, Bonati M. Risk classification systems for drug use during pregnancy: are they a reliable source of information? *Drug Saf*. 2000;23:245-253.
2. Kramer JM. Managing the risks of therapeutic products: proceedings of a workshop. *Pharmacoepidemiol Drug Saf*. 2005;14:619-628.
3. Andrews E, Gilsenan A, Cook S. Therapeutic risk management interventions: feasibility and effectiveness. *J Am Pharm Assoc (2003)*. 2004;44:491-500.

4. Lenz W, Knapp K. Thalidomide embryopathy [in German]. *Dtsch Med Wochenschr*. 1962;87:1232-1242.
5. Lenz W. A short history of thalidomide embryopathy. *Teratology*. 1988;38:203-215.
6. McBride WG. The teratogenic action of drugs. *Med J Aust*. 1963;41:689-692.
7. Daemmrich A. A tale of two experts: thalidomide and political engagement in the United States and West Germany. *Soc Hist Med*. 2002;15:137-158.
8. Sheskin J. Thalidomide in the treatment of lepra reactions. *Clin Pharmacol Ther*. 1965;6:303-306.
9. Larkin M. Low-dose thalidomide seems to be effective in multiple myeloma [editorial]. *Lancet*. 1999;354:925.
10. Munshi NC, Barlogie B, Desikan KR, et al. Novel approaches in myeloma therapy. *Semin Oncol*. 1999;26(5)(suppl 13):28-34.
11. Raje N, Anderson K. Thalidomide—a revival story. *N Engl J Med*. 1999;341:1606-1609.
12. Eleutherakis-Papaiakovou V, Bamias A, Dimopoulos MA. Thalidomide in cancer medicine. *Ann Oncol*. 2004;15:1151-1160.
13. Matthews SJ, McCoy C. Thalidomide: a review of approved and investigational uses. *Clin Ther*. 2003;25:342-395.
14. Franks ME, Macpherson GR, Figg WD. Thalidomide. *Lancet*. 2004;363:1802-1811.
15. Okafor MC. Thalidomide for erythema nodosum leprosum and other applications. *Pharmacotherapy*. 2003;23:481-493.
16. Wu JJ, Huang DB, Pang KR, et al. Thalidomide: dermatological indications, mechanisms of action and side-effects. *Br J Dermatol*. 2005;153:254-273.
17. Uhl K, Cox E, Rogan R, et al. Thalidomide use in the US: experience with pregnancy testing in the STEPS programme. *Drug Saf*. 2006;29:321-329.
18. Layton AM. Optimal management of acne to prevent scarring and psychological sequelae. *Am J Clin Dermatol*. 2001;2:135-141.
19. Larsen TH, Jemec GB. Acne: comparing hormonal approaches to antibiotics and isotretinoin. *Expert Opin Pharmacother*. 2003;4:1097-1103.
20. Lammer EJ, Chen DT, Hoar RM, et al. Retinoic acid embryopathy. *N Engl J Med*. 1985;313:837-841.
21. Centers for Disease Control and Prevention. Birth defects caused by isotretinoin—New Jersey. *MMWR Morb Mortal Wkly Rep*. 1988;37:171-172, 177.
22. Dermatologic Drugs Advisory Committee. Open public hearings on NDA 18-662 Accutane (isotretinoin capsules) [transcript]. US Dept of Health and Human Services. April 26, 1988.
23. Pastuszak A, Koren G, Rieder MJ. Use of the retinoid pregnancy prevention program in Canada: patterns of contraception use in women treated with isotretinoin and etretinate. *Reprod Toxicol*. 1994;8:63-68.
24. Atanackovic G, Koren G. Fetal exposure to oral isotretinoin: failure to comply with the Pregnancy Prevention Program. *CMAJ*. 1999;160:1719-1720.
25. Anderson JE, Ebrahim S, Floyd L, et al. Prevalence of risk factors for adverse pregnancy outcomes during pregnancy and the preconception period—United States, 2002-2004. *Matern Child Health J*. 2006;10(suppl 5): S101-S106.
26. Cooper WO, Hickson GB, Ray WA. Prescriptions for contraindicated category X drugs in pregnancy among women enrolled in TennCare. *Paediatr Perinat Epidemiol*. 2004;18:106-111.
27. Katz HI, Waalen J, Leach EE. Acitretin in psoriasis: an overview of adverse effects. *J Am Acad Dermatol*. 1999;41(3, pt 2):S7-S12.
28. Jesitus J. iPLEDGE now under way, despite objections. *Dermatology Times*. April 1, 2006. http://dtasia.advanstar.com/dtasia/News/iPLEDGE-now-under-way-despite-objections/ArticleStandard/Article/detail/317277. Accessed May 13, 2008.
29. Hill MJ. iPLEDGE: protecting patients or prohibiting access to care [editorial]? *Dermatol Nurs*. 2006;18:124.
30. Stein G; US Food and Drug Administration. Docket: 02N-0115—Risk management of prescription drugs; public hearing comment number EC-7. http://www.fda.gov/ohrms/dockets/dockets/02n0115/02n-0115-EC-7.htm. Published June 21, 2002. Accessed May 13, 2008.
31. Zavodny M. Fertility and parental consent for minors to receive contraceptives. *Am J Public Health*. 2004;94: 1347-1351.
32. McNulty PJ, Stanwood FM, Gallas SM. Parental consent for minors to receive contraceptives. *Am J Public Health*. 2005;95:191-192.
33. Jones RK, Boonstra H. Confidential reproductive health services for minors: the potential impact of mandated parental involvement for contraception. *Perspect Sex Reprod Health*. 2004;36:182-191.
34. *Felix v Hoffman-La Roche Inc*, 540 So2d 102, 105 (Fl 1989).
35. *Gerber v Hoffman-La Roche Inc*, 392 F Supp 2d 907 (SD Tx 2005).
36. *Banner v Hoffman-La Roche Inc and Roche Laboratories Inc*, 891 A2d 1229 (NJ Super Ct App Div 2006).
37. Kendall C, Afable-Munsuz A, Speizer I, et al. Understanding pregnancy in a population of inner-city women in New Orleans—results of qualitative research. *Soc Sci Med*. 2005;60:297-311.
38. Gilliam ML, Warden M, Goldstein C, et al. Concerns about contraceptive side effects among young Latinas: a focus-group approach. *Contraception*. 2004;70:299-305.
39. Harvey SM, Henderson JT, Thorburn S, et al. A randomized study of a pregnancy and disease prevention intervention for Hispanic couples. *Perspect Sex Reprod Health*. 2004;36:162-169.
40. Solorio MR, Yu H, Brown ER, et al. A comparison of Hispanic and white adolescent females' use of family planning services in California. *Perspect Sex Reprod Health*. 2004;36:157-161.

41. Thorburn S, Bogart LM. African American women and family planning services: perceptions of discrimination. *Women Health*. 2005;42:23-39.
42. Heit JA. The epidemiology of venous thromboembolism in the community: implications for prevention and management. *J Thromb Thrombolysis*. 2006;21:23-29.
43. Jick SS, Kaye JA, Russmann S, et al. Risk of nonfatal venous thromboembolism with oral contraceptives containing norgestimate or desogestrel compared with oral contraceptives containing levonorgestrel. *Contraception*. 2006;73:566-570.
44. Wu O, Robertson L, Langhorne P, et al. Oral contraceptives, hormone replacement therapy, thrombophilias and risk of venous thromboembolism: a systematic review. Thrombosis: Risk and Economic Assessment of Thrombophilia Screening (TREATS) Study. *Thromb Haemost*. 2005;94:17-25.
45. Wu O, Robertson L, Twaddle S, et al; Thrombosis: Risk and Economic Assessment of Thrombophilia Screening (TREATS) Study. Screening for thrombophilia in high-risk situations: a meta-analysis and cost-effectiveness analysis. *Br J Haematol*. 2005;131: 80-90.
46. Mohllajee AP, Curtis KM, Martins SL, et al. Does use of hormonal contraceptives among women with thrombogenic mutations increase their risk of venous thromboembolism? a systematic review. *Contraception*. 2006;73:166-178.
47. Samuelsson E, Hedenmalm K, Persson I. Mortality from venous thromboembolism in young Swedish women and its relation to pregnancy and use of oral contraceptives —an approach to specifying rates. *Eur J Epidemiol*. 2005;20:509-516.
48. Chaudhry V, Cornblath DR, Corse A, et al. Thalidomide-induced neuropathy. *Neurology*. 2002;59:1872-1875.
49. Wu JJ, Huang DB, Pang KR, et al. Thalidomide: dermatological indications, mechanisms of action and side-effects. *Br J Dermatol*. 2005;153:254-273.
50. Kaiser Daily Women's Health Policy. 122 pregnancies reported among women participating in Accutane iPLEDGE program. http://www.kaisernetwork.org/daily_reports/print_report.cfm?DR_ID=46599&dr_cat=2. Published August 1, 2007. Accessed May 13, 2008.