1-1-2016

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Recommended Citation

Stancil, S. L., Miller, M. K., Briggs, H., Lynch, D., Goggin, K., Kearns, G. Contraceptive Provision to Adolescent Females Prescribed Teratogenic Medications. *Pediatrics* 137, (2016).

Contraceptive Provision to Adolescent Females Prescribed Teratogenic Medications

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abstract

BACKGROUND AND OBJECTIVES: Rates of adult women receiving contraceptive provision when simultaneously prescribed a known teratogen are alarmingly low. The prevalence of this behavior among pediatric providers and their adolescent patients is unknown. The objective of this study was to describe pediatric provider behaviors for prescribing teratogens concurrently with counseling, referral, and/or prescribing of contraception (collectively called contraceptive provision) in the adolescent population.

METHODS: A retrospective review was conducted examining visits in 2008–2012 by adolescents aged 14 to 25 years in which a known teratogen (US Food and Drug Administration pregnancy risk category D or X) was prescribed. The electronic medical records were queried for demographic information, evidence of contraceptive provision, and menstrual and sexual histories. The data were analyzed using standard statistical methods.

RESULTS: Within 4172 clinic visits, 1694 females received 4506 prescriptions for teratogenic medications. The most commonly prescribed teratogens were topiramate, methotrexate, diazepam, isotretinoin, and enalapril. The subspecialties prescribing teratogens most frequently were neurology, hematology-oncology, and dermatology. Overall, contraceptive provision was documented in 28.6% of the visits. Whites versus nonwhites and older versus younger girls were more likely to receive contraceptive provision. The presence of a federal risk mitigation system for the teratogen also increased the likelihood of contraceptive provision.

CONCLUSIONS: Our data demonstrate female adolescents prescribed teratogens receive inadequate contraception provision, which could increase their risk for negative pregnancy outcomes. Although the presence of a federal risk mitigation system appears to improve contraceptive provision, these systems are costly and, in some instances, difficult to implement. Efforts to improve provider practices are needed.

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Ms Stancil conceptualized and designed the study, analyzed and interpreted the data, and drafted the initial manuscript; Dr Miller assisted with design of the study and interpretation of the data and reviewed and revised the manuscript; Dr Briggs assisted with collection and analysis of the data and reviewed the manuscript; Dr Lynch assisted with initial conceptualization of the study and reviewed and revised the manuscript; Dr Goggin assisted with design of data

WHAT'S KNOWN ON THIS SUBJECT: Adolescents in the United States have high rates of unintended pregnancy and may be prescribed medicines of teratogenic potential. The frequency of reproductive health counseling by pediatric providers to female adolescents prescribed these medications isnot known.

WHAT THIS STUDY ADDS: Adolescents prescribed known teratogens are receiving suboptimal reproductive health care. Our data illustrate that provider interventions must focus not only on sexual behaviors and the need for contraceptive care but also should include education regarding teratogenic risk associated with treatment.

To cite: Stancil SL, Miller M, Briggs H, et al. Contraceptive Provision to Adolescent Females Prescribed Teratogenic Medications. *Pediatrics*. 2016;137(1):e20151454

TABLE 1 Teratogenic Medications Queried for During Study Period

albendazole	enalapril	losartan	rosuvastatin
alprazolam	etoposide	lovastatin	simvastatin
amiodarone	fluconazole	megestrol	sirolimus
atenolol	fluvastatin	mercaptopurine	spironolactone
atorvastatin	griseofulvin	methimazole	tazarotene
azathioprine	imatinib	methotrexate	temozolomide
bosentan	irinotecan	misoprostol	tetracycles
captopril	isotretinoin	mycophenolate acid	thalidomide
carbamazepine	itraconazole	mycophenolate mofetil	thioguanine
clonazepam	leflunomide	paroxetine	topiramate
cyclophosphamide	letrozole	penicillamine	topotecan
dasatinib	lisinopril	phenytoin	valproic acid
diazepam	lithium	pitavastatin	voriconazole
divalproex sodium	lomustine	pravastatin	warfarin
efavirenz	lorazepam	ribavirin	

All medications listed were queried in females. Thalidomide was the only medication queried in males.

Limited data are available regarding prescribing of contraception to adolescents who have been concurrently prescribed a drug with known teratogenic potential (ie, teratogens). To communicate the potential teratogenic risk of a medication to the prescriber, the US Food and Drug Administration (FDA) currently uses an evidence-based grading system as part of product labeling that categorizes medications by potential for teratogenic risk (eg, category A are those with no demonstrated risk, categories D and X are those associated with definite risk and positive evidence of fetal harm).[1]

Several studies of family and internal medicine providers demonstrated low rates (20%–48%) of contraception provision among females of reproductive age prescribed teratogens.[1–4] However, no previous study has evaluated practices among pediatric providers or examined rates of documentation of sexual history or menstrual history in adolescents prescribed teratogens. To address this knowledge gap, we conducted a targeted, retrospective assessment of contraception provision in a large cohort of adolescent females prescribed potential teratogens.

METHODS

Study Design

A single-center, retrospective audit of data available in the electronic medical record (EMR) was conducted at a large Midwestern academic pediatric medical center. The study was approved by hospital institutional review board and was determined to be exempt from informed consent or assent requirements.

Selection of Participants

EMR data from female patients aged 14 to 25 years who were prescribed a known teratogen at hospital discharge or as an outpatient between January 1, 2008, and December 31, 2012, were included in this study. A total of 59 drugs labeled by the FDA as pregnancy risk categories D or X comprised the drug list (see Table 1). This list is not inclusive of all medications labeled as Category D or X by the FDA but rather a select group chosen based on preliminary inquiry of high-risk medications commonly prescribed at the pediatric medical center. Data from male patients aged 14 to 25 years who were prescribed thalidomide (a drug with paternal reproductive health guidance issued by the manufacturer to reduce teratogenic risk)[5,6] were also eligible for inclusion. Data were excluded from patients in whom the teratogen was prescribed for inpatient use only, as were those for patients prescribed a single dose of fluconazole for treatment of vulvovaginitis. Data from patients receiving fluconazole for >1 day were included in the analysis.

Data Collection and Outcome Measures

Encounters during which a teratogen was prescribed were queried for any documentation of contraceptive counsel (via key word search described later in the article or *International Classification of Diseases, 9th Revision*, codes V25.xx or V45.5), contraceptive prescription (via order indicating new prescription or documentation in medication list indicating prescription at previous visit) or referral for contraceptive care (via key terms search or order available in EMR). The pediatric specialty responsible for teratogenic prescription was also denoted (nephrology, hematology-oncology, etc.). Documentation of sexual history and menstrual history was determined based on key term search. Demographic data (age, gender, race, insurance status) were also recorded for each encounter during which a teratogen was prescribed. Separate analyses were performed on medications associated with formal federal surveillance programs, such as iPLEDGE and Risk Evaluation and Mitigation Strategy (REMS). These systems are used by the FDA when additional safety measures are needed beyond the professional labeling to ensure benefits of the medication outweigh risks, particularly with documented evidence of severe birth defects (ie, teratogenicity).[7] On the basis the assessment of risk completed by the FDA and agreement with manufacturer, there are various methods employed when a REMS is put into place, including, but not limited to, letters sent to prescribers, training requirements

TABLE 2 Terms Used in Automated Key Term Search

Contraceptive Counsel	Contraceptive Referral	Sexual History	Menstrual History
contraception	refer for contraception	sex	menarche
contraceptive	refer for birth control	vaginal	menses
condom	follow up for contraception	sexually active	last menstrual period
birth control	follow up for birth control	sexual activity	LMP
abstinence	refer to OBGYN	intercourse	
barrier protection	follow up with OBGYN	coitus	
LARC	refer for Depo-Provera	coitarche	
Plan B	refer for contraceptive	same sex	
emergency contraception	follow up for contraceptive	homosexual	
emergency contraceptive	refer for discussion of birth control		
OCP	refer for Depo-Provera		
Implant	refer for OCP		
NuvaRing	refer for IUD		
Nexplanon	refer for NuvaRing		
Implanon	refer for Nexplanon		
Mirena	refer for Implanon		
IUD	refer for Implant		
Depo Provera	follow up for discussion of birth control		
	follow up for Depo-Provera		
	follow up for OCP		
	follow up for IUD		
	follow up for NuvaRing		
	follow up for Nexplanon		
	follow up for Implanon		
	follow up for Implant		

IUD, intrauterine device; LMP, last menstrual period; OCP, oral contraceptive pills.

for prescribers, and information disseminated via professional organizations.

To facilitate EMR review, we created a list of key terms and performed an automated EMR search via full text index for these terms to identify contraception provision and sexual/menstrual histories. The list (Table 2) was developed by an multidisciplinary team of content experts and was intended to capture terms that would affirm documentation of contraceptive counsel, referral, sexual history, or menstrual history while optimizing efficiency of a large retrospective review. If ≥1 key terms were found within the documents specific to the encounter during which the teratogen was prescribed, the encounter was deemed to have documentation of the respective outcome measure (contraceptive counsel, referral, sexual history, or menstrual history). To validate the novel automated key term search strategy, we randomly selected 200 encounters from the original 4172 and performed a manual review of the EMR to serve as the reference standard. One author reviewed each of 200 encounters followed by review by a second author. Any discrepancies were resolved by consensus between these 2 authors. This subset size was chosen to limit manual annotation burden while ensuring a robust sample size for comparison of the automated key term search strategy with manual review. We determined sensitivity, specificity, positive predictive value, and negative predictive value along with 95% confidence intervals (CIs) to access validity of the automated search strategy.

Data Analysis

Data were analyzed by using Excel 2007 (Microsoft Corporation, Redmond, WA) and SPSS Statistics version 20 (IBM Corporation, Armonk, NY) to inform standard statistical measures along with OpenEpi and Vasserstats.[8,9] χ^2 test was used to evaluate comparisons between groups (eg, contraceptive provision documented in younger vs older patients). Relative risk (RR) assessment, including assessment of 95% confidence limits, was used to infer clinical significance associated with key findings. Multivariate regression analysis was also completed to identify variables that were predictive of receipt of contraceptive provision. The significance level set for all statistical analyses was $\alpha = 0.05$.

RESULTS

We identified 1694 female patients aged 14 to 25 who received 4506 prescriptions for teratogenic medications over the course of 4172 clinic visits (ie, encounters). No males received a prescription for thalidomide. The 5 most commonly prescribed teratogens (in decreasing frequency) were topiramate, methotrexate, diazepam, isotretinoin, and enalapril (see Fig 1). The 3 pediatric specialties prescribing teratogens with highest frequency were neurology, hematology-oncology, and dermatology (see Fig 2). Contraceptive provision was documented in 15.6%, 28.0%, and 46.9% of their encounters, respectively. Overall, contraceptive provision (ie, counsel, prescription, or referral) was documented in 1194 of 4172 (28.6%) encounters. Prescriptions for contraception (or documentation of current use) were present in 11% of encounters.

Of the 1694 females, 74% were white, 13% were black, and 7% were Hispanic, followed by smaller fractions of other ethnicities. The mean age of the patients in this study was 15.9 years (SD 1.6). Certain patient groups were identified as being more likely to receive contraceptive provision compared with their peers: whites

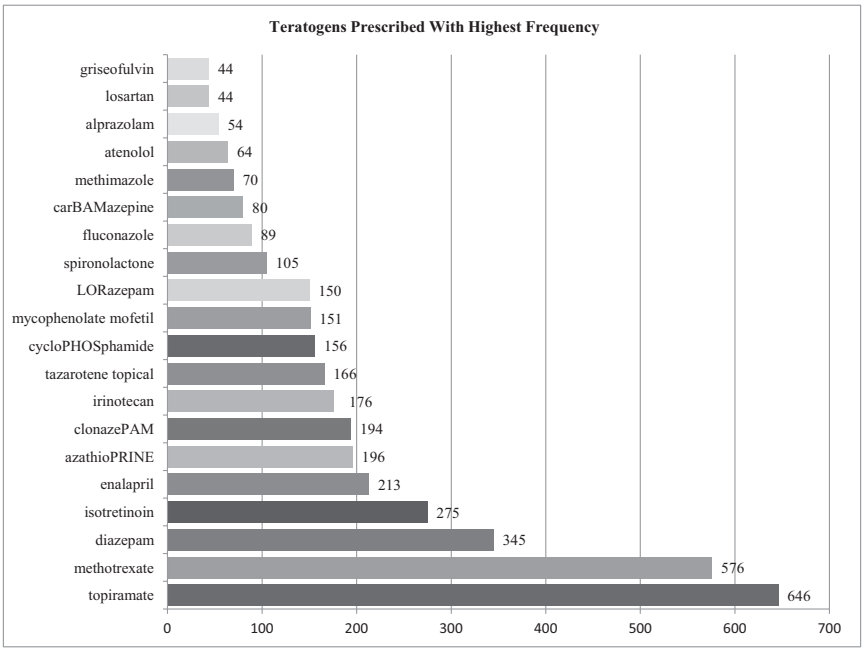

FIGURE 1
Twenty most commonly prescribed teratogens. Quantity indicates number of encounters during which the teratogen was prescribed.

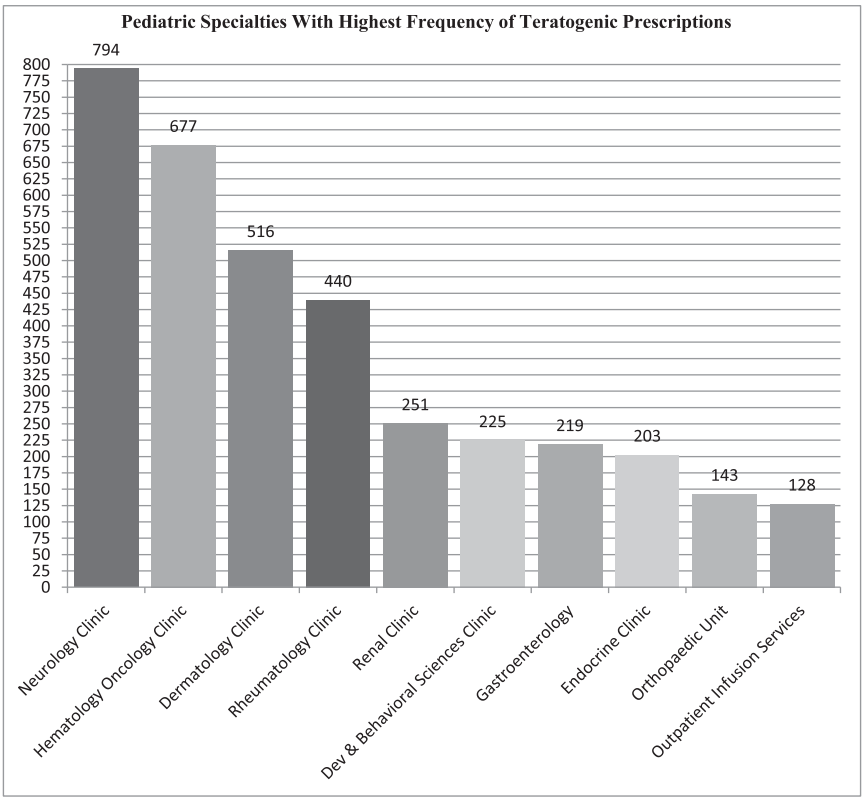

FIGURE 2
Pediatric specialty responsible for prescription of teratogen. Quantity indicates number of encounters during which a teratogen was prescribed.

versus nonwhites (RR 1.61, 95% CI, 1.41–1.83), older (≥16 years) versus younger girls (14–15 years; RR 1.20, 95% CI, 1.09–1.33), and those with either Medicaid or no insurance versus those with private commercial insurance (RR 1.09, 95% CI, 0.99–1.21). The presence of a federal surveillance system for the prescribed teratogen (eg, iPLEDGE or REMS) increased the chances of a patient receiving contraceptive provision (RR 2.09, 95% CI, 1.88–2.32). The presence of a federal surveillance system for a prescribed teratogen was associated with less frequent documentation of menstrual (RR 0.49, 95% CI, 0.37–0.69) and sexual histories (RR 0.56, 95% CI, 0.43–0.74) at that visit. Prescribers of teratogens were more likely to document a sexual history in younger girls compared with older girls (RR 1.34, 95% CI, 1.18–1.51). All of the aforementioned comparisons were statistically significant as determined by χ^2 tests (see Table 3). To identify variables that were predictive of receipt of contraceptive provision while controlling for confounders, multivariate regression analysis was performed, and adjusted odds ratios (aOR) were calculated. Age ≥16 years, race, year of visit, noncommercial insurance coverage (Medicaid or no insurance), and presence of REMS were all significant predictors of receipt of contraceptive provision (see Table 4).

The sensitivity, specificity, positive predictive value, and negative predictive value of the automated key term search method for each of the 4 categories are summarized in Table 5. Overall, the automated method performed well in all 4 categories with sensitivity ranging from 88% to 100% and specificity ranging from 90% to 100%. Two terms appeared to explain the majority of discrepancies identified between the automated key term search method and the manual review. The term “implant” included

in the contraceptive counsel key term category was documented in the context of a noncontraceptive surgical implant, such as vagal nerve stimulator "implant" or cardiac pacemaker "implant." The automated key term search strategy found "implant' in 11 such cases (of 55 total positives found via automated key term search) as affirmation of contraceptive counsel due to the nonspecific nature of this term. Also, "sex" was a term listed in the sexual history category that affirmed documentation of sexual history in 8 cases (of 49 total positives found via automated key term search) where actual documentation was described as simply sex at birth (ie, female or male).

DISCUSSION

Previously published data reveal that rates of women receiving contraception counseling and/or prescription who have been prescribed a teratogen by an adult care provider are alarmingly low. One study of a family practice resident clinic evaluated contraceptive counseling provided to women aged 15 to 44 years who were also prescribed a teratogen and found the rate of documented contraceptive counseling to be 46%.[4] This increased to 80% after an educational intervention was introduced. Another study evaluated contraceptive counseling in women of reproductive age prescribed drugs in FDA categories A and B compared with those in the D or X category. The rates of contraceptive counseling between the groups were similar, and thus women in the study prescribed a known teratogen were at increased risk for fetal harm during pregnancy compared with women prescribed nonteratogenic medications.[1] In another study evaluating practices of ambulatory care providers prescribing potential teratogenic drugs in women aged 14 to 44 years, contraceptive counseling was documented in only 20% of cases.[2] Collectively, these previous studies illustrate that women of reproductive age who were prescribed a known teratogen were no more likely to receive contraceptive counseling than women prescribed a medication with low or absent teratogenic risk.

Our study underscores that this missed opportunity for reproductive health counseling extends to the adolescent female population. Less than one-third of our adolescent cohort prescribed a teratogen had documentation of contraceptive provision. Of these patients, only 11% received or were currently using some sort of prescribed contraceptive medication or device. Factors such as white race and coverage by Medicaid or no insurance were predictive of contraceptive provision. This evidence was demonstrated first by χ^2 analysis and strengthened after

TABLE 3 Descriptive Comparison Between Subgroups of Patients Prescribed a Teratogen ($N = 4172$ Encounters, Unless Otherwise Stated)

Comparison	Percentage	χ^2	*P*
Contraceptive provision among whites vs non-whites	31.9% whites, 19.9% non whites	58.43	<.001
Contraceptive provision among older (≥16 y) vs younger (14–15 y)	30.9% older, 25.7% younger	13.42	<.001
Contraceptive provision among Medicaid or no insurance vs commercial insurance ($N = 4159$, 13 missing)	30.1% non-commercial, 27.6% commercial	3.2	.037
Contraceptive provision with presence of federal risk mitigation system	53.7% REMS, 25.7% non-REMS	148.4	<.001
Menstrual history with federal risk mitigation system	14.2% non-REMS, 6.9% REMS	17.4	<.001
Sexual history with federal risk mitigation system	19.7% non-REMS, 11.1% REMS	18.7	<.001
Sexual history among younger (14–15 y) vs older (≥16 y)	21.9% younger, 16.4% older	20.3	<.001

TABLE 4 Variables Predictive of Contraceptive Provision

Variable	aOR (95% CI)	*P*
Age ≥16 y	1.30 (1.13–1.50)	<.001
Race (reference = white)		
Black	0.35 (0.28–0.45)	<.001
Hispanic	0.81 (0.60–1.10)	.17
Asian	0.49 (0.23–1.10)	.08
Other	0.47 (0.33–0.67)	<.001
Year of visit (ascending)	1.26 (1.18–1.33)	<.001
Non-commercial Insurance	1.22 (1.05–1.42)	<.01
REMS	3.33 (2.69–4.11)	<.001

aOR, adjusted odds ratio.

TABLE 5 Data Validation of Automated Key Term Search Strategy

Category	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Contraceptive counsel	98% (85%–99.8%)	90% (84%–94%)	71% (57%–82%)	99% (96%–99.9%)
Sexual history	95% (82%–99%)	94% (88%–97%)	80% (65%–89%)	99% (95%–99.7%)
Menstrual history	88% (69%–97%)	100% (97%–100%)	100% (82%–100%)	98% (95%–99.5%)

Only 1 encounter met requirements for contraceptive referral by automated search method and manual review; agreement was 100% between the methods; however, statistical analysis is limited because of the low prevalence of this condition. PPV, positive predictive value; NPV, negative predictive value.

controlling for confounding variables as described by multivariate analysis. Year of visit was also predictive of receipt of contraceptive provision. In fact, each year after 2008 (beginning of study period) conferred a 26% increase in contraceptive provision compared with preceding year. The higher occurrence of contraceptive provision in our older patients (16–25 years) may have been driven by a bias held by some pediatric providers regarding a perceived low incidence of sexual intercourse[10–12] and, by inference, lower teratogenic risk in younger girls (ie, 14–15 years). However, this assumption is inconsistent with established literature.

According to the National data from the 2013 Youth Risk Behavior Surveillance System, 35.2% of adolescent females (grades 9–12, typical age 14–18 years) were classified as currently sexually active (ie, having had sex in past 3 months), and 15.7% of the these females reported not using any method to prevent pregnancy during their more recent sexual encounter. Only 29.8% of these females reported contraceptive (ie, birth control pills, patch, ring, injection, IUD, or implant) use, and 53.1% reported condom use to prevent pregnancy before/during their last sexual encounter. Also, 28% of ninth graders (typical age 14–15 years) and 41.7% of tenth graders reported at least 1 episode of sexual intercourse in their lifetime.[13] This information highlights the importance of recognizing the early onset of sexual activity in young females and the commensurate increased risk for pregnancy and poor fetal outcome when these patients are prescribed a drug with known teratogenic potential absent their receiving appropriate education/warning. Clearly, such harm may be preventable through prudent intervention by health care providers and purposeful education when medications with significant teratogenic potential are prescribed. Of note, our study did not specifically evaluate the prevalence of sexually active females in our adolescent cohort but rather evaluated whether a sexual history had been documented by the provider (ie, asking the question about history of any previous sex regardless of answer).

Many of the teratogenic medications queried in this study are used for treatment of chronic disease states (eg, cyclophosphamide, mycophenolate-containing products, azathioprine, methotrexate for immunosuppression; isotretinoin for severe acne; topiramate for chronic migraine prophylaxis). Often, less teratogenic options may not be available to the prescriber or appropriate for the patient. Therefore, adequate discussion and subsequent document of reproductive health counseling is imperative in this at-risk population.

Federal surveillance systems have the potential to improve rates of contraceptive provision and mitigate potential adverse effects of teratogenic drugs. Our findings strengthen the evidence by describing an increase in documentation of contraceptive provision in this subgroup. However, in our study, adolescents prescribed teratogens associated with federal surveillance systems were less likely to have documentation of sexual and menstrual histories. This finding was unexpected given that the focus of these systems is to proactively reduce the risk of unplanned pregnancy during drug treatment. Simply, the availability of these systems would seemingly prompt the prescriber to actively engage in contraceptive provision. Our findings also illustrate that in a large study cohort, contraceptive provision (in its broadest sense) does not appear to be documented and, therefore, is not likely adequately addressed by health care providers. Potential reasons for this are many (eg, fear or bias associated with the assessment of menstrual or sexual history in young adolescents, inadequate knowledge regarding teratogenic risks, concern over identifying a positive risk behavior, inadequate knowledge of adolescent reproductive health best practices, especially among subspecialists). For example, a recent study reported that time constraints, confidentiality issues, and comfort level were cited by health care providers as major limitations to providing sexual health care to adolescents in an emergency department setting.[14] Despite these barriers, it is our contention that failure to document a sexual history for an adolescent who is prescribed a medication that carries a high risk of fetal harm should pregnancy occur is unacceptable. In the recent policy statement, the American Academy of Pediatrics urged pediatricians to "conduct a developmentally-targeted sexual history … and provide appropriate screening and/or education about safe and effective contraceptive methods."[15] The statement also urged pediatricians to be familiar with counseling, insertion, and/or referral for long-acting reversible contraceptive options (eg, implant and intrauterine device). These recommendations underscore the role of the pediatrician, both primary care provider and subspecialist, in promoting optimal reproductive health care to adolescents, particularly those prescribed medications with known teratogenic potential.

Our study used the FDA pregnancy risk category D or X to classify medications with evidence of teratogenic potential. However, this current classification system has been criticized for its oversimplification of complicated information regarding risks and benefits of using medications during pregnancy and lack of inclusion of discussion for use in patients of

reproductive potential. To address this long-standing concern expressed by clinicians and scientists, the FDA recently developed the pregnancy and lactation labeling final rule (PLLR), which was published in December 2014. The PLLR will abolish the current pregnancy risk category designation (A, B, C, D, or X) and incorporate a monograph with discussion of current evidence regarding safety in not only pregnancy and lactation but also in patients of reproductive potential. The reproductive health subsection will include "information, when necessary, about the need for pregnancy testing, contraception recommendations, and information about infertility as it relates to the drug."[16] This change will provide prescribers more detailed information (ie, "talking points") regarding risks versus benefits of these medications when prescribed to adolescents of reproductive potential. After full incorporation into the PLLR, the teratogenic medications chosen for this analysis will carry more comprehensive information based on available evidence to aid in future reproductive health counseling.

A few caveats are important to note when interpreting the findings of our study. The retrospective approach involves inherent limitations; however, this design was chosen because it was the most appropriate methodology to accomplish our initial inquiry and, specifically, to determine if a problem existed with regard to the prescribing of potential teratogens. The data captured in this study are, by their nature, limited to documentation by providers. For example, the automated key search terms with >1 meaning, such as "implant" and "sex," had the potential to confound our findings. Modifying these 2 terms within the automated key term search method via discrete definition would likely further improve specificity, as well as positive predictive value of the novel method used to query our medical records. Accordingly, it is possible that verbal contraceptive provision was provided but was not adequately recorded in the EMR. Finally, our study did not identify and exclude patients with developmental delay or significant cognitive impairment who may have a more limited need for contraceptive provision based on the severity of their neurologic deficit.

CONCLUSIONS

Documentation of contraceptive provision among female adolescents prescribed teratogens by pediatric providers is low; only 28.6% of study participants received this critical care. Opportunity exists in these adolescents to increase rates of contraceptive counsel, the prescription of contraception if appropriate, or referral for such care when it becomes necessary to use a medication with known teratogenic potential. Female adolescents and their parents should be educated regarding the teratogenic risk of the medications prescribed to them and counseled on safe and effective reproductive choices. These prescriber-patient interventions should be adequately documented in the medical record. Prescriber education is also warranted to increase knowledge of commonly prescribed medications and systems/approaches currently available to mitigate their potential serious adverse effects, including teratogenicity. Further studies evaluating the efficacy of such interventions, both educational and systems based, are warranted.

ACKNOWLEDGMENTS

We thank Kelly Behr for invaluable assistance with database design.

ABBREVIATIONS

CI: confidence Interval
EMR: electronic medical record
FDA: US Food and Drug Administration
PLLR: pregnancy and lactation labeling final rule
REMS: Risk Evaluation and Mitigation Strategy
RR: relative risk

validation method and interpretation of the data and reviewed and revised the manuscript; Dr Kearns provided critical review of study design, data analysis, and interpretation and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

DOI: 10.1542/peds.2015-1454

Accepted for publication Sep 2, 2015

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: Supported by the Divisions of Adolescent and Emergency Medicine and the Departments of Pediatrics and Research Development, Children's Mercy Hospital, Kansas City, MO.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

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Pediatrics 2016;137;
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