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Low Rates of Pregnancy Screening in Adolescents Before Teratogenic Exposures in a National Sample of Children's Hospitals

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CONFLICT OF INTEREST DISCLOSURES

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AUTHOR CONTRIBUTIONS

Pooja Rao: Responsibility for the integrity of the data and the accuracy of the data analysis; study concept and design; acquisition, analysis, or interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; statistical analysis; and funding. Yimei Li: Acquisition, analysis, or interpretation of data; critical revision of the manuscript for important intellectual content; and statistical analysis. Kelly D. Getz: Acquisition, analysis, or interpretation of data; critical revision of the manuscript for important intellectual content; and statistical analysis. Tamara P. Miller: Acquisition, analysis, or interpretation of data and critical revision of the manuscript for important intellectual content. Yuan-Shung Huang: Acquisition, analysis, or interpretation of data and critical revision of the manuscript for important intellectual content. Jennifer J. Wilkes: Acquisition, analysis, or interpretation of data and critical revision of the manuscript for important intellectual content. Alix E. Seif: Critical revision of the manuscript for important intellectual content. Rochelle Bagatell: Critical revision of the manuscript for important intellectual content and administrative, technical, or material support. Brian T. Fisher: Critical revision of the manuscript for important intellectual content and administrative, technical, or material support. Clarisa Gracia: Study concept and design; acquisition, analysis, or interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; and study supervision. Richard Aplenc: Responsibility for the integrity of the data and the accuracy of the data analysis; study concept and design; acquisition, analysis, or interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; funding; administrative, technical, or material support; and study supervision.

Abstract

BACKGROUND—Adolescents with cancer engage in sexual behaviors and are exposed to teratogenic chemotherapy. There are no data regarding pregnancy screening patterns for adolescents before chemotherapy exposure.

METHODS—A cross-sectional study of leukemia and emergency room (ER) admissions in the Pediatric Health Information System from 1999 to 2011 was conducted. Females who were 10 to 18 years old and 1) had newly diagnosed acute lymphoblastic leukemia (ALL) or acute myeloid leukemia (AML) or 2) had ER visits with computed tomography (CT) of the abdomen/pelvis were included. The exposure was a hospital visit with either chemotherapy or an abdominal/pelvic CT scan. The main outcome was a pregnancy test billed on the same day or before the teratogenic exposure within the same index admission. Log-binomial regressions were used to compute prevalence ratios and 95% confidence intervals comparing pregnancy screening in the leukemia and ER cohorts.

RESULTS—A total of 35,650 admissions were identified. The proportion of visits with an appropriately timed pregnancy test was 35%, 64%, and 58% in the ALL (n=5889), AML (n = 127), and ER cohorts (n = 34,634), respectively. Patients with ALL were significantly less likely to have a pregnancy test than the ER cohort (adjusted prevalence ratio, 0.71; 95% confidence interval, 0.65–0.78), but there was no significant difference between the AML and ER cohorts (adjusted prevalence ratio, 1.12; 95% confidence interval, 0.99–1.27). There was substantial hospital-level variation in pregnancy screening patterns.

CONCLUSIONS—Adolescents with acute leukemia and ER visits have low rates of pregnancy screening before teratogenic exposures. Standardized practice guidelines for pregnancy screening among adolescents may improve screening rates.

Keywords

acute lymphoblastic leukemia; acute myeloid leukemia; adolescent; cross-sectional studies; pregnancy tests

INTRODUCTION

Although the epidemiology of pregnancy in adolescents with acute leukemia is poorly defined, the United States consistently has one of the highest adolescent pregnancy rates in the world.¹ Furthermore, nearly all chemotherapy agents used for childhood/adolescent leukemia belong to Food and Drug Administration pregnancy category C (animal studies have shown an adverse effect on the fetus, although there are no adequate or well-controlled studies in pregnant women) or D (adequate studies have demonstrated a human fetal risk).² This combination of factors has the potential for catastrophic outcomes for pregnant adolescents with leukemia. Moreover, identifying pregnancy in adolescents before chemotherapy initiation has challenges. Clinicians typically are not adept at identifying risky sexual behaviors among youth with chronic illnesses, including cancer.^{3–11} Pregnancy can also be easily overlooked, particularly in adolescence, because the symptoms are often nonspecific.

Because of the potential clinical significance of pregnancy in adolescent cancer patients, routine pregnancy screening before chemotherapy initiation seems reasonable. However, there are no clear guidelines regarding pregnancy screening in adolescents with cancer. Recent Children's Oncology Group clinical trial protocols for acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) include guidelines for pregnancy screening before chemotherapy initiation, but they are written in a general manner with varied and nonspecific wording.

In emergency medicine, pregnancy screening protocols exist for adolescents before the receipt of radiation via imaging studies because of the known teratogenic risks of radiation. These institutional protocols are based on the recommendations of radiology societies such as the American College of Radiology.¹² Although these guidelines exist, one study suggests that adolescents exposed to computed tomography (CT) radiation have lower than expected rates of pregnancy screening.¹³ This study has not been confirmed by other reports.

Given this lack of data, we sought to investigate pregnancy screening patterns among adolescents with ALL and AML versus adolescents with an emergency room (ER) visit who received a CT scan of the abdomen and/or pelvis; we used data from the Pediatric Health Information System (PHIS) database. We also performed a subanalysis that investigated whether enrollment in Children's Oncology Group clinical trial AAML0531 was associated with pregnancy screening for patients with AML.

MATERIALS AND METHODS

Study Design and Data Source

Data for this study were obtained from PHIS, an administrative database that contains inpatient, emergency department, ambulatory surgery, and observation encounter– level billing data from not-for-profit, freestanding pediatric hospitals in the United States.^{14,15} The hospitals included in this study were primarily urban, academic hospital centers affiliated with major medical centers. The PHIS hospital size varies from 100 to 500 beds. These hospitals are affiliated with the Children's Hospital Association (Overland Park, Kan). Data quality and reliability are ensured through a joint effort between the Children's Hospital Association and participating hospitals. Portions of the data submission and data quality processes for the PHIS database are managed by Truven Health Analytics (Ann Arbor, Mich). For the purposes of external benchmarking, participating hospitals provide discharge/encounter data, including demographics, diagnoses, and procedures. Nearly all of these hospitals also submit resource utilization data (eg, pharmaceutical, imaging, and laboratory data) to PHIS. Data are deidentified at the time of data submission, and data are subjected to a number of reliability and validity checks before they are included in the database. For this study, data from 43 hospitals were included.

Human Patient Protection

According to the institutional review board of the Children's Hospital of Philadelphia, this study was not considered human subjects research.

Cohort Selection

There were 3 distinct cohorts established with PHIS admission-level data. The first 2 were acute leukemia cohorts that included female adolescents with newly diagnosed ALL or AML who were receiving induction chemotherapy during their index admission. Patients with ALL or AML were identified with a combination of *International Classification of Diseases, Ninth Revision*, diagnosis codes and a manual review of induction chemotherapy exposures, as previously validated.^{14,15}

The third cohort was composed of female adolescents with ER site visits undergoing a CT scan of the abdomen and/or pelvis. Because of radiology department institutional protocols requiring pregnancy screening before radiation exposure, the ER cohort was thought to represent the best available patient population for comparing pregnancy screening in an acute leukemia cohort. PHIS billing codes for radiology imaging were used to capture CT scans of the abdomen and/or pelvis.

Patients within the 3 cohorts who were 10 to 18 years old and had admission dates between January 1, 1999 and September 30, 2011 were eligible for inclusion. The lower end of the age range used for cohort assembly was chosen to ensure the inclusion of patients at the normal age of menarche.^{16,17}

Patients with acute leukemia who received a CT scan of the chest, abdomen, or pelvis anytime during the induction chemotherapy admission were excluded because of the difficulty in determining whether these patients received a pregnancy test on account of the CT scan or chemotherapy initiation. Patients with duplicate medical record numbers between cohorts were excluded (Fig. 1).

Exposure

The exposure was a hospital visit with a teratogenic exposure for patients with newly diagnosed ALL or AML or an ER visit with a CT scan of the abdomen and/or pelvis.

Outcome

The primary outcome was an appropriately timed pregnancy test, which was defined as a pregnancy test billed on the same day as or before the first chemotherapy exposure (for the leukemia cohorts) or a CT scan of the abdomen and/or pelvis (for the ER cohort) within the same index admission. The outcome was defined with PHIS Clinical Transaction Classification (CTC) codes for pregnancy testing.

Covariates

The covariates included the cohort type, which was categorized as ER, ALL, or AML. Patient age was analyzed as a dichotomous variable (10–13 vs 14–18 years) in descriptive analyses and as a categorical variable by the unit of year (10–18 years) in regression models. Race was categorized as white, black, or other (Asian, American Indian, multiple/other, unknown, or missing). The insurance type was categorized as private, public, or other (self-pay, other, or missing). The admit year was analyzed as a categorical variable by the unit of year (1999–2011). The hospital center was analyzed as a categorical variable.

In a subanalysis of patients with AML, AAML0531 clinical trial enrollment was analyzed as a covariate to determine the association of enrollment with pregnancy screening.¹⁸ The probabilistic merge of AAML0531 has been described previously.¹⁹

Statistical Analysis

Patient demographics were summarized by frequencies and proportions for each cohort and were compared with chi-square tests. Log-binomial regressions were used to compute unadjusted and adjusted prevalence ratios comparing pregnancy screening in the leukemia cohorts with pregnancy screening in the ER cohort. Results were summarized as prevalence ratios and 95% confidence intervals. The generalized estimating equation (GEE) method was used to account for hospital center clustering. Models were adjusted via the GEE method and for any confounding covariate in the univariate analysis. The evaluated covariates included age, race, insurance, and admit year. Each covariate was added independently to the unadjusted model, and the change in the prevalence ratio for the primary exposures of interest (ALL or AML vs ER) was assessed. A change 10% was considered evidence of meaningful confounding, and covariates exhibiting such a change were retained in the final adjusted model.

Trends in cohort-specific pregnancy screening prevalences by admit year and age were evaluated graphically. To determine whether screening differences between cohorts were modified over the study period, prevalence ratio comparisons were evaluated within strata of the admit year. A chi-square test was used to compare pregnancy screening proportions by the AAML0531 enrollment status.

Because point-of-care (POC) pregnancy testing would not be captured in PHIS, a bias analysis was performed to evaluate the potential impact of unobserved POC pregnancy testing. Corrected prevalence ratios were estimated for a range of sensitivities in the ascertainment of pregnancy screening among the compared cohorts, with the ER cohort used as the reference.

Statistical analyses were performed with Stata 12 (StataCorp LP, College Station, Texas). A 2-sided *P* value less than .05 was considered statistically significant.

RESULTS

Between January 1, 1999 and September 30, 2011, 35,650 patient admissions were captured in the 3 cohorts. Table 1 presents baseline demographic characteristics for the 3 cohorts. The 3 cohorts differed significantly with respect to age and race. Patients with ALL were younger and more likely to be white in comparison with AML and ER patients.

The proportion of visits with an appropriately timed pregnancy test was 35%, 64%, and 58% in the ALL, AML, and ER cohorts, respectively. The unadjusted prevalence ratios comparing pregnancy screening rates with respect to the ER cohort were 0.60 (95% confidence interval, 0.55–0.65) for the ALL cohort and 1.09 (95% confidence interval, 0.96–1.24) for the AML cohort. In the AML subanalysis, no association was found between

AAML0531 clinical trial enrollment and appropriately timed pregnancy screening (63.6% screening for enrolled patients vs 64.9% screening for unenrolled patients; $P = .9$).

Figure 2 illustrates the difference in the proportions of appropriately timed pregnancy tests by patient age for each cohort. Although overall screening increased in all 3 cohorts with increasing age, the ALL cohort had a lower proportion of appropriately timed pregnancy tests in comparison with the ER and AML cohorts for nearly all ages. Figure 3 illustrates hospital center–specific proportions of pregnancy screening for the 3 cohorts. There was considerable center-level variability in the proportions of pregnancy screening. In addition, the intracenter screening prevalences were not consistent across the 3 cohorts.

In a GEE model adjusted for hospital clustering and patient age (a confounder in the univariate analysis), patients with ALL were still significantly less likely to have an appropriately timed pregnancy test in comparison with the ER cohort (adjusted prevalence ratio, 0.71; 95% confidence interval, 0.65–0.78). In a GEE model adjusted for hospital clustering, patients with AML were more likely to have an appropriately timed pregnancy test in comparison with the ER cohort, although the results did not achieve statistical significance (adjusted prevalence ratio, 1.12; 95% confidence interval, 0.99–1.27).

In evaluating trends in cohort-specific screening by the admit year, we found that screening in the ALL cohort appeared to increase over time, whereas the prevalence of screening in the AML and ER cohorts was relatively stable from 2008 onward (Fig. 4). Both the ALL and ER cohorts appeared to have greater screening overall for all ages in contemporary years versus earlier admit years (Supporting Figs. 1 and 2 [see online supporting information]). To determine whether differences in screening between cohorts were modified over the study period, prevalence ratio comparisons were evaluated within strata of the admit year. In comparison with the ER cohort, the admit year–specific prevalence ratios for the ALL cohort appeared to increase in contemporary years versus earlier years, although AML admit year–specific prevalence ratios did not appear to follow such a trend (Supporting Table 1 [see online supporting information]).

POC pregnancy testing was assumed to cause decreased ascertainment of pregnancy screening by PHIS pregnancy-test billing data (Supporting Tables 2 and 3 [see online supporting information]). Across multiple scenarios in which POC testing was assumed to occur more frequently in the ER cohort than either the ALL or AML cohort, the results of the bias analyses suggested that the observed prevalence ratios comparing pregnancy testing in the ALL and AML cohorts with the ER cohort were biased upward. Specifically, an adjustment for such differential underascertainment demonstrated that the magnitude of the actual relative difference in the frequency of pregnancy testing between the leukemia and ER cohorts was generally more extreme than observed, with both the ALL and AML cohorts being less likely to have an appropriately timed pregnancy test than the ER cohort.

DISCUSSION

This study found low proportions of pregnancy screening among adolescents with ALL, AML, and ER visits with abdominal/pelvic CT radiation exposures in a nationally

representative sample of patients at freestanding pediatric hospitals. Remarkably, the prevalence of appropriately timed pregnancy tests across these 3 patient groups ranged from 30% to 60%. In particular, adolescents with ALL were 30% less likely to have an appropriately timed pregnancy test than their ER counterparts. No statistical difference between proportions of appropriately timed pregnancy tests was found between the AML and ER cohorts.

The reason for the difference in ALL and AML pregnancy screening prevalences versus ER screening prevalences is not known. Because ALL therapy is less intensive than AML therapy, physicians may omit pregnancy screening in patients with ALL, even though both ALL chemotherapy and AML chemotherapy are Food and Drug Administration pregnancy category C or D. Although increasing age is associated with increased screening, regardless of cohort, patient age does not seem to be a factor in explaining the higher screening in the AML cohort versus the ER cohort.

Although previously reported in the literature, the low rate of pregnancy screening in adolescents before abdominal radiation exposure was surprising. A study by Goyal et al^{13,20} found that only 37% of adolescents were screened for pregnancy before CT and that the proportions of pregnancy screening in women of reproductive-age exposed to teratogenic medications in the ER setting were low. Our work corroborates these findings in a larger, more contemporary patient sample with a more inclusive adolescent age range. This study indicated that although the proportion of screening was higher in the ER cohort compared with the ALL cohort, only 58% of ER patient visits had pregnancy screening. Notably, secular trends in testing for both cohorts have increased in recent years (Supporting Table 1 and Supporting Figs. 1 and 2 [see online supporting information]), and this may represent increased adherence to guidelines or perhaps an increased willingness on the part of physicians and adolescent patients to discuss sexual health practices. Regardless, our results highlight a need to improve pregnancy screening not only among adolescents with leukemia but also among adolescents in other clinical settings where teratogenic exposures exist.

The hospital center-level variation in pregnancy screening was another notable finding (Fig. 3). Variation in pregnancy screening existed not only between hospitals but also within a hospital by cohort type (ALL, AML, and ER). Although earlier studies suggested regional variation in pregnancy screening^{13,21} and practice variation across centers has also been described for supportive-care measures such as analgesia administration in pediatric cancer patients,^{22,23} to our knowledge, no prior reports have demonstrated different intracenter practice variation in pregnancy screening. Future work should focus on elucidating the factors responsible for both intercenter and intracenter variation in pregnancy screening, such as academic hospital status, hospital volume, affiliation with an adult hospital, and hospital environment (urban vs rural).

Our findings highlight a need for standardized pregnancy screening practices for adolescent patients exposed to teratogens, including those with acute leukemia. Although pregnancy screening guidelines before chemotherapy initiation exist in some recent Children's Oncology Group protocols, these recommendations are vague and inconsistent. This inconsistency may have contributed to the interhospital and intrahospital screening variation

observed in our data (Fig. 3). Because of challenges in identifying pregnant adolescents by history alone, routine, standardized pregnancy testing is clinically imperative. Improvements in pregnancy screening adherence may be facilitated by standardized institutional supportive care guidelines addressing pregnancy screening guidelines. Such guidelines would require a thoughtful discussion of the possible benefits and disadvantages of testing. For example, although mandated monthly pregnancy screening in adolescents before chemotherapy exposure would minimize teratogenic risk, this strategy may not be cost-effective, particularly for patients with long hospital stays. Regardless of the final recommendation, the presence of such a recommendation may reduce the marked practice variability observed in our data.

Importantly, the low rate of pregnancy testing may bespeak a reluctance to have discussions surrounding sexual health between pediatric oncology providers and adolescent patients. This reluctance may be due to physician discomfort as well as hesitancy on the part of the patient to disclose this information. Parental presence may also be a barrier to allowing such conversations to happen. We hope that the discussion of standardized screening guidelines would encourage dialogue about sexual health. The increased prevalence of pregnancy testing in contemporary years in the ALL cohort may also be an indication of an improvement in such conversations happening. Pediatric oncologists are well positioned to have discussions about sexual health with patients because of the frequent, longitudinal course of visits that accompanies oncologic treatment; this creates time for trust to develop between the patient and the provider. Communication training may aid in initiating discussions about sexual practices in a way that also fits into the context of a busy oncology clinic visit. Sexual health discussions between physicians and patients also have implications beyond identifying high-risk sexual behaviors. National statistics indicate that nonconsensual sexual activity occurs not infrequently,²⁴ and this further increases the importance of open communication regarding sexual experiences in adolescent oncology patients.

Although the large sample size and national representation of this study are substantial strengths, several weaknesses must be acknowledged. First, because of cohort data availability, this study was restricted to admit years 1999–2011. Thus, current pregnancy screening trends could not be assessed. Second, because this study was limited to PHIS-contributing centers, the results may not be generalizable to pediatric practices embedded within adult institutions. Although such embedded pediatric practices may have smaller clinical volumes, the close proximity to medical services treating adults may heighten the awareness of pregnancy issues. Lastly, outcome ascertainment was a limitation because POC pregnancy tests are not captured in PHIS. The reduced sensitivity of PHIS billing data was hypothesized to be a greater concern for the ER cohort because of the larger volume of pregnancy tests performed in an ER versus an oncology floor. However, the bias analysis results are supportive of the observed prevalence ratios being biased upward for both the ALL and AML cohorts in comparison with the ER cohort (Supporting Tables 2 and 3 [see online supporting information]).

In conclusion, our data suggest that adolescents exposed to teratogens in the health care setting are not consistently screened for pregnancy. This can lead to undetected pregnancies

with serious downstream consequences for the adolescent mother and fetus. These findings support the need for standardized pregnancy screening guidelines among adolescents with acute leukemia and those exposed to ionizing radiation to ensure consistent testing.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Cohort creation flowchart. ALL indicates acute lymphoblastic leukemia; AML, acute myeloid leukemia; CT, computed tomography; ER, emergency room.

Figure 2.
Cohort-specific prevalence of appropriately timed pregnancy tests by patient age. ALL indicates acute lymphoblastic leukemia; AML, acutemyeloid leukemia; ER, emergency room.

Figure 3.

Cohort-specific prevalence of appropriately timed pregnancy tests by hospital center. The centers are organized in the order of increasing screening based on the ER cohort. ALL indicates acute lymphoblastic leukemia; AML, acute myeloid leukemia; ER, emergency room.

Figure 4.

Cohort-specific prevalence of appropriately timed pregnancy tests by admit year. ALL indicates acute lymphoblastic leukemia; AML, acute myeloid leukemia; ER, emergency room.

TABLE 1

Patient Demographics for Each Cohort

Demographic	ER Cohort (n = 34,634)	ALL Cohort (n = 889)	AML Cohort (n = 127)	P (χ^2)
Age, No. (%)				<.0001
10–13 y	13,474 (39)	511 (57)	56 (44)	
14–18 y	21,160 (61)	378 (43)	71 (56)	
Race, No. (%)				<.0001
White	24,011 (69)	668 (75)	80 (63)	
Black	6,211 (18)	78 (9)	15 (12)	
Other ^a	4,412 (13)	143 (16)	32 (25)	
Insurance, No. (%)				.07
Private	14,388 (42)	374 (42)	55 (43)	
Public	11,890 (34)	333 (37)	47 (37)	
Other ^b	8,356 (24)	182 (21)	25 (20)	

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; ER, emergency room.

^a Other includes Asian, American Indian, multiple/other, unknown, and missing.^b Other includes self-pay, other, and missing.