Exclusion of Women of Childbearing Potential in Clinical Trials of Type 2 Diabetes Medications: A Review of Protocol-Based Barriers to Enrollment

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EPIDEMIOLOGY/HEALTH SERVICES RESEARCH

OBJECTIVE

Women of childbearing potential are often excluded from participating in clinical trials owing to concerns about adverse fetal effects of treatment. This study aims to determine the prevalence of fertility-related exclusion criteria in clinical trials of type 2 diabetes medications and to determine whether these criteria are commensurate with drug risk.

RESEARCH DESIGN AND METHODS

ClinicalTrials.gov was queried for trials of type 2 diabetes medications that were phase 2 or 3, were based in the U.S., and enrolled participants 18–40 years old. Six hundred eighty-eight trials met criteria. Information collected about each trial included enrollment, trial length, exclusion and inclusion criteria, trial sponsor, and pregnancy category of drug(s) administered.

RESULTS

Most studies (59%) included one or more fertility-related exclusion criteria, most often excluding current pregnancy (55%) and breast-feeding (44%). Trials of medications with increased fetal risk were not more restrictive: trials of category C drugs (evidence of fetal risks in animals) were less likely to exclude pregnancy compared with trials of category B drugs (no known human or animal fetal risks) (45.6% vs. 69.8%, odds ratio [OR] 0.37 [95% CI 0.20, 0.65], *P* = 0.0005) or to require contraceptive use (29.9% vs. 57.1%, OR 0.32 [95% CI 0.18, 0.56], *P* = 0.001).

CONCLUSIONS

In clinical trials of type 2 diabetes medications, exclusion criteria affecting women of childbearing potential are often disproportionate to risk to the participant and fetus. These criteria have the potential to impede young women's access to clinical trials and may hinder the acquisition of clinical knowledge critical for improving the care of women with diabetes.

Type 2 diabetes is a leading cause of morbidity, mortality, and health care expenditure in the U.S., and it is highly prevalent in both men and women (1). Women ages 25–44 years with diabetes have a death rate triple that of unaffected women, and their risk of cardiovascular disease and blindness is higher than that of affected men (2). Despite the urgent need for treatment options for young women with diabetes,

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adequate enrollment of women of childbearing potential in clinical trials remains an ongoing challenge (3).

The U.S. has a long history of limiting participation of women in clinical research. In the early 20th century, studies generally ignored sex-based differences in pharmacology and used a "typical 70-kilogram man" as the reference standard (4). The thalidomide tragedy of the 1950s both highlighted a need for better testing of medications in pregnancy and, simultaneously, intensified precautions against enrollment of reproductive-age women in clinical trials. In 1977, the U.S. Department of Health and Human Services recommended that women of childbearing potential be routinely excluded from clinical trials both out of concern for fetal welfare and to restrict liability (5). This stance was reversed in 1993 when the U.S. Department of Health and Human Services determined that its prior recommendations were "rigid and paternalistic" and had the effect of limiting equitable participation of women in early drug development studies. They suggested that women of childbearing potential be included in trials provided they took precautions against pregnancy and received information about drug risks (6). In addition, the National Institutes of Health (NIH) Revitalization Act of 1993 mandated that studies receiving NIH funding include women in numbers sufficient for analyzing sex differences and stated that "women of childbearing potential should not be routinely excluded from participation in clinical research." (7)

Currently, principal investigators are allowed a significant amount of freedom to determine when to exclude women of childbearing potential or when to enact limitations on their participation, such as requiring contraceptive use. A number of studies have investigated restrictions to participation of pregnant women in clinical trials (8–10), but few studies have investigated the barriers that are routinely placed on women of childbearing potential (11,12). The goal of this study is to determine the extent of such barriers among registered trials and to assess whether the level of restriction is concordant with the risk of trial medications. Diabetes was selected as the condition of interest due to its high prevalence and its significance in pregnancy.

RESEARCH DESIGN AND METHODS

ClinicalTrials.gov was queried for trials meeting each the following criteria: phase 2 or 3, interventional, pharmaceutical, related to type 2 diabetes, based in the U.S., and enrolling at least some female participants between 18 and 40 years old. This age range was selected to represent women of childbearing potential, since women under 40 years of age account for 97% of pregnancies in the U.S. (13). Age 18 years was set as the lower limit because studies in pediatric populations are subject to different regulatory restrictions (14). ClinicalTrials.gov has been available since February 2000, and the earliest trial included in this study began in 1995. Information collected about each trial included number of enrolled participants (enrollment), length of subject participation (enrollment length), trial length between start-up and close out (recruitment length), exclusion criteria, inclusion criteria, trial sponsor (investigator-initiated or pharmaceutical), and pregnancy category of drug(s) administered. Recruitment length was included as a parameter of interest in order to assess whether certain inclusion or exclusion criteria might prolong recruitment, as more exclusive protocols by their nature have a smaller pool of qualified participants. Drug category information was obtained from the FDALabel program on www.fda.gov.

Specific data collected on exclusion criteria were as follows: whether the trial excluded all women, all women of childbearing potential, pregnant women, breast-feeding women, or women planning to donate ova. Trials that excluded all women or all women of childbearing potential were not considered in groupings of other exclusion criteria (e.g., excluding pregnancy). Inclusion criteria collected included requirements for contraceptive use before, during, and after participation in the trial and requirements to comply with pregnancy testing. Trial registrations that featured any of the above inclusion or exclusion criteria were categorized as having "at least one fertility-related criterion."

Trials were then grouped by the category of drug administered. Pregnancy category B indicates that there is no proven risk to the fetus in animal studies. Category C has evidence of adverse fetal effects in animal models but without well-controlled trials showing harm in humans. Category D indicates known adverse fetal effects in human studies. Category X indicates contraindication in pregnancy, with risks significant enough to outweigh the benefits of use in pregnancy in almost all circumstances (15). Some trials administered multiple drugs, and these were grouped according to the highest-risk drug given; e.g., "at least one category D drug" includes all trials that have at least one category D drug but no category X drugs. Trials administering drugs without a pregnancy category were grouped as "at least one unknown drug." Sponsor of the trial was determined by the trial registration to be either a pharmaceutical company– or an investigator-initiated trial, usually an investigator at an academic health center.

Statistical Analysis

Counts for exclusion criteria are reported as frequencies and percentages. Continuous variables, such as enrollment length and recruitment length, are reported as median and interquartile range (IQR) (25th and 75th percentiles). Exclusion criteria for each of the higher risk drug categories were compared with the "B only" drug category via logistic regression using the profile penalized likelihood approach (16). Results from logistic regression are reported as odds ratio (OR), CI, and *P* value. Distribution-free multiple comparison methods (17) were used to compare the higher-risk groups with "B only" for continuous outcomes. Investigator-initiated and pharmaceutical company–sponsored trials were compared via Fisher exact test for binary outcomes and Wilcoxon rank sum test for continuous outcomes.

RESULTS

The study requirements of the 688 trials that met search criteria are shown in Table 1. Four hundred and two (58.4%) studies included at least one fertility-related criterion including 51 (7.4%) that excluded all women of childbearing potential and 350 (54.9%) that excluded current pregnancy. Particularly restrictive criteria, such as excluding women planning to donate ova (2.7%), requiring two contraceptives (2.8%), and requiring contraceptives after the end of the

Table 1—Study requirements of clinical trials involving type 2 diabetes medications by drug category: *N* = 688

	Total	Category B drugs only	At least one category C drug	At least one category D drug	At least one category X drug	At least one unknown drug
n	688	64	277	18	10	319
Enrollment	300.0 (105.0, 555.0)	290.0 (112.0, 501.0)	420.0 (189.5, 662.5)	102.5 (86.0, 704.0)	210.0 (130.0, 604.0)	229.0 (87.0, 421.0)
Enrollment length (weeks)[a]	24.0 (12.0, 26.0)	18.0 (10.0, 26.0)	26.0 (22.0, 30.0)**	24.0 (12.0, 28.0)	56.0 (45.5, 90.0)**	16.0 (12.0, 26.0)
Recruitment length (years)[b]	1.4 (1.0, 2.1)	1.4 (1.0, 2.1)	1.5 (1.1, 2.2)	2.5 (1.2, 3.6)	2.0 (0.8, 2.7)	1.3 (0.8, 2.0)
Exclusion criteria						
Includes ≥1 fertility-related criteria	402/688 (58.4)	45/64 (70.3)	128/277 (46.2)**	11/18 (61.1)	10/10 (100.0)*	208/319 (65.2)
Excludes all women	5/688 (0.7)	0/64 (0.0)	0/277 (0.0)	0/18 (0.0)	1/10 (10.0)*	4/319 (1.3)
Excludes all women of childbearing potential	51/688 (7.4)	1/64 (1.6)	3/277 (1.1)	0/18 (0.0)	2/10 (20.0)*	45/319 (14.1)**
Excludes pregnancy	350/637 (54.9)	44/63 (69.8)	125/274 (45.6)**	11/18 (61.1)	8/8 (100.0)	162/274 (59.1)
Excludes lactation	278/637 (43.6)	37/63 (58.7)	100/274 (36.5)**	8/18 (44.4)	4/8 (50.0)	129/274 (47.1)
Excludes plans to donate eggs	17/637 (2.7)	0/63 (0.0)	1/274 (0.4)	0/18 (0.0)	0/8 (0.0)	16/274 (5.8)
Contraceptive requirements						
Requires 1 contraceptive	213/637 (33.4)	36/63 (57.1)	82/274 (29.9)**	7/18 (38.9)	3/8 (37.5)	85/274 (31.0)**
Requires 2 contraceptives	18/637 (2.8)	0/63 (0.0)	1/274 (0.4)	0/18 (0.0)	1/8 (12.5)*	16/274 (5.8)*
Accepts abstinence	63/231 (27.3)	10/36 (27.8)	17/83 (20.5)	4/7 (57.1)	0/4 (0.0)	32/101 (31.7)
Requires contraceptives prior to enrollment	13/637 (2.0)	2/63 (3.2)	5/274 (1.8)	1/18 (5.6)	0/8 (0.0)	5/274 (1.8)
Length of time (weeks) contraceptives required prior to enrollment	6.0 (6.0, 12.0)	9.0 (6.0, 12.0)	6.0 (6.0, 6.0)	12.0 (12.0, 12.0)	N/A	12.0 (12.0, 12.0)
Requires contraceptives after trial end	41/637 (6.4)	3/63 (4.8)	10/274 (3.6)	0/18 (0.0)	1/8 (12.5)	27/274 (9.9)
Length of time (weeks) contraceptives required after trial end	4.0 (2.0, 4.0)	2.0 (2.0, 4.0)	3.0 (2.0, 4.0)	N/A	4.0 (4.0, 4.0)	4.0 (4.0, 5.0)
Requires multiple pregnancy tests	29/637 (4.6)	5/63 (7.9)	12/274 (4.4)	2/18 (11.1)	0/8 (0.0)	10/274 (3.6)

Data are *n* trials having the criteria/total *N* trials (%). Continuous outcomes are reported as median (25th, 75th) percentile. N/A, not applicable. *$P < 0.05$ compared with B only. **$P < 0.01$ compared with B only.
[a]Enrollment length is the duration of subject participation in a trial. [b]Recruitment length is the measure of time between the start-up and close out of the trial.

trial (6.4%), were not uncommon. A total of 29 trials (4.6%) required multiple pregnancy tests to continue participation in the trial (Table 1). This requirement was most common in trials of category C drugs (11.1%) and least common in trials of category D drugs (0%). Recruitment length was similar for all groups (Table 2).

Compared with trials of category B drugs only, those with category C drugs were less likely to exclude current pregnancy (OR 0.37 [95% CI 0.20, 0.65], P = 0.0005) or to require contraceptive use (OR 0.32 [95% CI 0.18, 0.56], P = 0.001). Category X drugs were significantly more likely than category B drugs to include at least one fertility-related criterion (OR 9.00 [95% CI 1.06, 1,178.6], P = 0.04), exclude all women of childbearing potential (OR 12.45 [95% CI 1.48, 148.8], P = 0.02), and require two contraceptives (OR 25.4 [95% CI 1.24, 3,848.7], P = 0.04). Compared with category B only, trials with at least one unknown category drug were more likely to exclude all women of childbearing potential (OR 7.02 [95% CI 1.83, 62.89], P = 0.002). However, they were less likely to require contraceptive use (OR 0.34 [95% CI 0.19, 0.59], P = 0.001).

As shown in Table 3, investigator-initiated trials had a significantly smaller enrollment (70.5 participants [IQR 40.0, 150.0] vs. 329.5 participants [138.0, 582.5], $P < 0.001$) and longer recruitment length (3.4 years [IQR 1.9, 4.7] vs. 1.3 years [IQR 0.9, 2.0], $P < 0.001$) compared with pharmaceutical company–sponsored trials, despite having a similar enrollment length (20.5 weeks [IQR 9.5, 50.0] and 24.0 weeks [IQR 12.0, 26.0]). Investigator-initiated trials were also significantly more likely to have at least one fertility-related criterion (78.6% vs. 56.1%, $P < 0.001$) and to exclude pregnancy (77.3% vs. 52.4%, $P < 0.001$).

The most frequently studied drug category was insulin (Supplementary Table 1). The most commonly studied drug was metformin (n = 111), followed by insulin glargine (Lantus) (n = 62), sitagliptin (n = 52), pioglitazone (n = 50), and exenatide (n = 45).

CONCLUSIONS

This study demonstrates that fertility-related exclusion criteria were common among phase 2 and 3 clinical trials of diabetes medications. Furthermore,

Table 2—Recruitment time of clinical trials involving type 2 diabetes medications by exclusion criteria: *N* = 688

	No fertility-related criteria	≥1 fertility-related criteria	Requires contraception	Excludes pregnancy	Excludes all women of childbearing potential	Excludes all women
Number of trials	286	402	231	350	51	5
Enrollment	291.0 (120.5, 561.0)	305.5 (102.0, 547.0)	357.0 (134.0, 600.0)	339.0 (120.0, 590.0)	120.0 (60.0, 260.0)	84.0 (63.0, 111.0)
Enrollment length (weeks)[a]	24.0 (12.0, 26.0)	24.0 (12.0, 30.0)	24.0 (12.0, 30.0)	24.0 (12.0, 48.0)	12.0 (4.0, 12.5)	16.0 (8.0, 23.0)
Recruitment length (years)[b]	1.3 (1.0, 2.1)	1.4 (1.0, 2.2)	1.5 (1.0, 2.1)	1.5 (1.1, 2.3)	0.9 (0.6, 1.3)	2.5 (1.2, 2.7)

Data are median (25th, 75th) percentile. [a]Enrollment length is the duration of subject participation in a trial. [b]Recruitment length is the measure of time between the start-up and close out of the trial.

exclusion criteria were often not proportionate with risk of medication teratogenicity. The most frequent exclusion criteria relating to women of childbearing potential included pregnancy, breastfeeding, and specific contraceptive requirements. Contraceptives continue to be routinely required by protocol (18,19), despite recommendations of the American College of Obstetricians and Gynecologists that requirements be based on risk of pregnancy (20). Participation of women in clinical trials remains inadequate, at <40%, and restrictions limiting the enrollment of pregnant women and women of childbearing potential are at least partly responsible for this disparity (21,22).

Compared with pharmaceutical company–sponsored trials, investigator-initiated trials were significantly smaller and were more likely to have at least one fertility-related criterion and to exclude pregnancy. One possible reason for this finding may be the close relationship between pharmaceutical companies and the U.S. Food and Drug Administration. Given this relationship, pharmaceutical companies may feel a stronger obligation or desire to recruit a representative sample in accordance with the NIH Revitalization Act. This trend may be related to requirements of individual institutional review boards (IRBs), which may impose increased requirements due to strong moral obligations to their communities and sensitivity to local context and community attitudes (23). Central IRBs are associated with faster review and decreased cost and may be better able to comply with federal policies on recruitment of women (23,24).

At least two major mechanisms could account for the lack of correlation between trial risk and protocol exclusivity. The first is variability in drug labeling, which may limit its utility in devising fair protocols. For example, exenatide carries risk of fetal loss, skeletal ossification defects, cleft palate, and reduced fetal growth while dapagliflozin is associated with mild fetal renal pelvis dilatation, and both of these drugs are category C. With such substantial variability in teratogenicity of drugs within one category, making informed decisions about risk based on these categorizations alone is challenging. For this reason and others, the U.S. Food and Drug

Table 3—Study requirements of clinical trials involving type 2 diabetes medications by sponsor type: *N* = 688

	Investigator initiated	Pharmaceutical company	*P*
Number of trials	70	618	
Enrollment	70.5 (40.0, 150.0)	329.5 (138.0, 582.5)	<0.0001
Enrollment length (weeks)[a]	20.5 (9.5, 50.0)	24.0 (12.0, 26.0)	0.72
Recruitment length (years)[b]	3.4 (1.9, 4.7)	1.3 (0.9, 2.0)	<0.0001
Inclusion and exclusion criteria			
Includes ≥1 fertility-related criteria	55/70 (78.6)	347/618 (56.1)	0.0003
Excludes all women	2/70 (2.9)	3/618 (0.5)	0.08
Excludes all women of childbearing potential	4/70 (5.7)	47/618 (7.6)	0.81
Excludes pregnancy	51/66 (77.3)	299/571 (52.4)	0.0001
Excludes lactation	31/66 (47.0)	247/571 (43.3)	0.60
Excludes plans to donate eggs	0/66 (0.0)	17/571 (3.0)	0.24
Contraceptive requirements			
Requires 1 contraceptive	18/66 (27.3)	195/571 (34.2)	0.33
Requires 2 contraceptives	0/66 (0.0)	18/571 (3.2)	0.24
Requires contraceptives prior to enrollment	1/66 (1.5)	12/571 (2.1)	1.00
Length of time (weeks) contraceptives required prior to enrollment	12.0 (12.0, 12.0)	6.0 (6.0, 12.0)	0.48
Requires contraceptives after trial end	0/66 (0.0)	41/571 (7.2)	0.02
Length of time (weeks) contraceptives required after trial end	N/A	4.0 (2.0, 4.0)	N/A
Requires multiple pregnancy tests	3/66 (4.5)	26/571 (4.6)	1.00

Data are reported as *N* trials having the criteria/total *N* trials (%) with Fisher exact test. Continuous outcomes are reported as median (25th, 75th) percentile with Wilcoxon rank sum test. N/A, not applicable. [a]Enrollment length is the duration of subject participation in a trial. [b]Recruitment length is the measure of time between the start-up and close out of the trial.

Administration is eliminating the lettered system and replacing it with a standardized summary of available drug safety data in pregnant women and animals (25). While the new system may facilitate improved understanding of drug risk, the original grading system has been in place since 1979, so changes in IRB protocol based on the new classification system are unlikely to be immediate.

Another possible reason for protocol restrictions disproportionate to risk is concern about liability both for the woman and for a potential pregnancy. Although liability is a legitimate concern, it does not supersede principles of equity and access in clinical research (26). In addition, if given the opportunity and provided with appropriate information, many pregnant women will opt to participate in clinical trials for both personal and altruistic reasons (9,27,28).

A limitation of this study was its reliance on ClinicalTrials.gov registration data. Previous studies suggest that these data may underestimate the true prevalence of some exclusion criteria, particularly pregnancy (10). We did not review each trial protocol to obtain further details related to the inclusion and exclusion of women of childbearing potential. However, it is clear that criteria affecting participation of women of childbearing potential occur at a frequency of at least the rates reported herein. We also did not systematically follow up on published studies or summary results posted on the ClinicalTrials.gov website to view actual enrollment data of women of reproductive age, as our initial review showed that most published trials did not provide enough details on demographics of study participants to determine what proportion were women of reproductive age. Thus trials may have been underpowered to detect differences in reproductive toxicity between treatment agents.

The exclusion of women of childbearing potential from clinical trials, either outright or through multiple restrictive criteria, may be detrimental to clinical practice. Limiting participation of young women decreases study generalizability, as the risk to young women and fetuses who will eventually receive treatments is largely unknown (29). Diabetes is one of the most common chronic conditions complicating pregnancy, and novel medications will be used in pregnancy whether or not sufficient data are available. Examination of exclusion criteria from other common disorders affecting women of reproductive age, such as hypertension and mood disorders, may shed further light on these practices.

Future studies should investigate the effects of restrictions on women of childbearing potential on enrollment in studies of other medical conditions that commonly affect younger women, such as rheumatologic disease, mood disorders, and epilepsy. Eliminating unnecessary barriers to recruitment will likely speed enrollment and increase generalizability of clinical trial data to women of all ages.

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