Unmet Demand for Highly Effective Postpartum Contraception in Two Cities in Texas

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For presentation at the Annual Meeting of the Population Association of America, Boston, MA, May 1-3, 2014.

Abstract:

The postpartum period represents a key opportunity for women to learn about and obtain effective contraception. We assess women's contraceptive preferences and use in the first 6 months after delivery. We conducted a prospective cohort study of 800 postpartum women, recruited from 3 hospitals in Austin and El Paso, Texas. Women age 18-44 who wanted to delay childbearing for at least 24 months were eligible for the study and completed interviews following delivery and at 3 and 6 months postpartum. At each interview, participants were asked what contraceptive method they would like to be using, as well as what method they were actually using. This study found considerable interest in LARC and permanent methods. However, there is substantial discordance between method preference and actual use. At 6 months postpartum, many more women would like to be using a highly effective method than have been able to do so.

Acknowledgement:

This study was carried out as part of the Texas Policy Evaluation Project with support from an anonymous foundation and an NICHD center grant (R24 HD042849).

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Although much is known about the mix of contraceptive methods in use in the United States, it is unclear whether the current mix actually reflects women's preferences. Many women who intend to limit their fertility or delay childbearing continue to rely on methods with relatively high typical-use failure rates such as oral contraceptives, condoms, and withdrawal. While use of long-acting reversible contraception (LARC) has increased over the last decade,(1) it has been argued persuasively that unintended pregnancy rates could be reduced if more women relied on highly effective methods.(2, 3) But the low utilization of LARC may not reflect the true underlying demand for the IUD and implant as several demonstration projects, particularly the CHOICE project in St. Louis, have shown a dramatic uptake in LARC when there is supportive counseling and the methods are provided at no cost.(4, 5) Demand for male and female sterilization may not be fully met either due to a variety of access barriers.(6-12)

According to the most recent round of the National Survey of Family Growth (NSFG), approximately half of all pregnancies in the U.S. are unwanted or mistimed, and 61% of all unintended pregnancies and 75% of unwanted births occur to women who have already had at least one live birth.(13) Furthermore, over half of all these unintended pregnancies occur within two years following delivery.(13) This is a time when women have access to the health care system, are often insured, and are frequently motivated to prevent a future pregnancy. In this paper, our objective is to determine the contraceptive methods women in two cities in Texas would like to be using in the postpartum period, as well as whether they are able to access their preferred method.

METHODS AND MATERIALS

This study was conducted shortly after the Texas state legislature drastically reduced funding for family planning, and many providers of subsidized family planning services had experienced substantial cuts in their budgets.(14) Participants were recruited after delivery at three hospitals: St David's Hospital in Austin, and University Medical Center and Las Palmas Hospital in El Paso. These hospitals were chosen to obtain a mix of publicly and privately insured participants, a variety of ethnic and socioeconomic groups, and to allow for differences in contraceptive provision by policy context, since the types and availability of public funding for family planning vary between the two cities. We aimed to enroll four hundred women in each city, 300 who were publicly insured and 100 who were privately insured at the time of delivery. Eligible participants were aged between 18 and 44 years, wanted no more children for at least two years at the time of recruitment, delivered a healthy singleton infant whom they expected would go home with them upon discharge, spoke English or Spanish, and lived in the United States within 50 miles of the hospital of recruitment. After obtaining signed informed consent from participants who agreed to take part in the study, we administered a 20-minute face-to-face interview baseline interview, in English or Spanish. Follow-up interviews were conducted by telephone at 3 months, 6 months, and 9 months postpartum. We offered an incentive payment of \$30 for completing the initial interview, and \$15 for completing each of the telephone interviews.

The initial (or baseline) questionnaire collected information on demographic and socioeconomic variables including age, parity, relationship status, ethnicity, education, insurance status, and income. Future childbearing intentions and contraceptive use were assessed at baseline and in each of the three succeeding interviews. Intentions were assessed using the question "Do you plan to have more children in the future?" Those who did want

more children were asked a follow-up question to assess the desired timing. In the baseline interview, participants were asked if they had had a tubal ligation, or an IUD or Implant had been inserted while they were in the hospital. At each successive interview, the contraceptive use questions refer to the full range of methods with a prompt for use of methods that might not be thought of as birth control such as abstinence, or a method that a spouse or partner was using. The very small number of women who stated that they were using two methods together were classified as using the most effective of the two methods (15).

One of the main purposes of the study was to track participants' preferences with respect to the type of contraception that they would like to be using. To do so, we designed a panel of questions asked over the course of the first three interviews. In the baseline and three-month postpartum interviews, we asked about the birth control method participants wanted to be using at six months postpartum. Both interviews also included a prompt asking for any method that the participant might have left out because it was too expensive or not covered by her insurance. In the six-month interview, women who had not mentioned LARC in response to any previous question were also asked "Would you consider using an IUD if it was offered free or for a small fee?" The same question was also asked about the implant. To ensure demand for sterilization was fully captured, women who had not previously expressed a desire for tubal ligation or vasectomy, and who did not want any more children or who did not know if they wanted more children in the future were also asked "Would you like to have had a tubal ligation in the hospital right after you had your new baby?" Finally, these same participants were asked, "Would you like your husband/partner to get a vasectomy?"

We distinguished between a participant's preferred contraceptive method given in response to the direct question, and another method that might have been mentioned as a response to any of the prompts, terming the latter a "latent preference". We then classified the preference and the latent preference into a four-tier hierarchy constructed according to method efficacy, following that detailed in Contraceptive Technology (16). The lowest tier, which we term "less effective methods" (LEM), includes methods where 18 or more pregnancies per 100 women per year would be expected with a typical use: condoms, withdrawal, spermicides, sponges, fertility-based awareness methods (including the rhythm method), and abstinence. The second tier, which we term "hormonal methods" (no women in our study were using or expressed a preference for the diaphragm) includes methods for which 6-12 pregnancies per 100 women per year can be expected with typical use: combined and progestin-only contraceptive pills, injectables, the vaginal ring, and the patch. The third tier includes highly effective long-acting reversible contraception (LARC): the implant, Copper-T IUD (ParaGard), and the levenogestrel releasing intrauterine system (Mirena IUD), while the fourth tier consists of permanent methods: female sterilization and vasectomy. If a participant expressed a latent preference for more than one method, for example both the implant and female sterilization, her preference was categorized based on the most effective method mentioned. Women who had a tubal ligation, or whose partners or spouses had a vasectomy were not asked for their method preferences, and were classified as having a preference for a permanent method.

In total, we recruited 803 participants who completed baseline interviews, 403 in Austin and 400 in El Paso. Overall, 672 (84%) participants completed all four interviews, and 709 (89)% completed the six-month interview on which the present analysis is focused. Of the women interviewed at six months postpartum, 12 had become pregnant and were thus

excluded. Sociodemographic characteristics, insurance status, and fertility intentions at baseline, and at six months postpartum were calculated separately by city. The statistical significance of differences between the Austin and El Paso cohorts was determined using Chi-squared tests of the homogeneity of proportions. Using the same four-tier categorization used for method preferences, we show actual use of contraception by method at three-month intervals up to nine moths postpartum for both cities combined. The remainder of the analysis is focused on the actual use of contraceptive methods, the expressed preference for contraceptive methods, and the difference between the two at sixmonths postpartum.

We show the proportions of respondents using each category of method at six months postpartum, the proportions with an unprompted preference for a method in the respective categories, and, finally, the latent preference structure based on the prompted questions (if applied) for each city. We again use Chi-squared tests of the homogeneity of proportions to test for the significance of differences between use and preference in each city, and to test for differences between cities in each of the three dimensions.

Finally, we conducted multivariable logistic regression analyses to explore factors associated with the demand for highly effective methods, and factors associated with actually obtaining and using such methods among women who expressed a preference for them. Since women who want to have another child at some point in the future (spacers) might be expected to have less interest in highly effective contraception in the postpartum period than women who do not plan to have another child (limiters), we conducted separate analyses in for each of these two groups. For spacers, the dependent variable in the first model was a preference for LARC, while for limiters it was a preference for either a long-acting or a permanent method (LAPM). In each case, we counted either an unprompted or a prompted

preference as a success, and included the following covariates: city, age group, parity, level of education, insurance status, relationship status, Hispanic ethnicity, and annual family income as covariates. The models of actual use at six months postpartum included the same covariates and were restricted to only those participants who had expressed a preference for LARC in the model for spacers, or LAPM in the model for limiters.

The target sample size for the study of 800 with 300 public and 100 private patients in each city was chosen with multiple analyses in mind since we planned to analyze prenatal and postpartum counseling, in addition to contraceptive preferences. With a projected cumulative loss to follow-up of 20%, the target sample size would allow us to test for a fifteen percentage point two-sided difference between proportions (from 0.7 to 0.55) between the two cities with power of 0.97, and an alpha level of 0.05. It would also permit us to test for a two-sided difference between public and private patients of the same magnitude with power of 0.9, and an alpha level of 0.05. All analyses were performed using Stata version 13.0. Human subjects approval for this study was obtained from the Institutional Review Boards at the University of Texas at Austin, the University of Texas at El Paso, St. David's Hospital in Austin, Texas, and University Medical Center and Las Palmas Hospital in El Paso, Texas.

RESULTS

Social and demographic characteristics of the study participants recruited in Austin and El Paso are shown in Table 1. The two cohorts are similarly distributed with respect to age, parity, relationship status, and insurance status, but differ with respect to ethnicity, education, and annual household income. The proportion Hispanic among Austin participants, while high, is lower than in El Paso where over 90% of participants reported

Hispanic ethnicity. There was a greater proportion with less than a high school education, but a lower proportion with an annual household income of less than \$10,000 in Austin as compared to El Paso. In the baseline interview shortly after delivery, the expressed desire to have additional children was similar in the two cities, but at 6 months the proportion wanting another child was greater in Austin than in El Paso.

The use of contraception by method category is shown in Figure 1 for both cities combined at each of the four interviews. Postpartum female sterilization accounts for all of the contraceptive use in the baseline interview. By three months, almost all participants were using some form of contraception. There was substantial use of LEM and hormonal methods, some uptake of LARC, and only a slightly greater proportion relying on sterilization than at baseline. This pattern changed, but only slightly, over the next six months. LEM continued to account for nearly 45% of all contraceptive use; hormonal use declined, and use of LARC and permanent methods both increased by small amounts.

Figure 2 shows both use and method preference at the six-month interview, separately for each city. Use by method was similar in Austin and El Paso (p = 0.349). In both cities, there was a substantial difference between the method being used at six months, and the method that the participant had said she would like to be using at that time three months earlier. The preference for use of both LARC and sterilization exceeded its actual use in both Austin and El Paso. There was, however, a small but significant difference between the two cities in the distribution of preferred methods with more women in Austin preferring LARC and more women in El Paso preferring hormonal methods and LEM.

Using the broader specification of preference that incorporated the various prompts regarding interest in LARC and permanent methods, which we have termed latent preference, the difference between preference and actual use widens considerably as shown

in the rightmost charts in Figure 2. The proportion of participants with a latent preference for LARC is 35% or more in both cities, as is the proportion with a latent preference for a permanent method. The difference in the latent preference distribution between the two cities was not significant (p=0.492).

Among women who wanted more children or were not sure about it, logistic multivariable regression analysis of the factors associated with a latent preference for LARC revealed a significant association with only two of the categorical variables included in the model (Table 2). Women over 30 wanting an additional child were less likely than younger women to prefer or have an interest in using a LARC method; also, Hispanic women were more likely to have a preference for or interest in LARC among spacers. The second model in Table 2 addressed the factors associated with actual use of LARC among the women in this group who had expressed a preference for or interest in LARC. Having more than a High School education, having retained insurance coverage, and Hispanic ethnicity were positively associated with actual use of LARC, while women age 30 or more had lower odds of using LARC. However, the largest and most significant coefficient in this model was for an annual family income exceeding \$75,000.

Similar models for the participants who wanted no more children are shown in Table 3 with regard to having a latent preference for, and then actually using either a long-acting or a permanent method (LAPM). In this group, being younger than 30 and having an annual family income exceeding \$35,000 were both negatively associated with a latent preference for LAPM. In the model for actual use of LAPM among women with a preference for or interest in LAPM and no desire for further childbearing, having lost insurance coverage since delivery was the sole significant predictor of use.

DISCUSSION

This study has pointed to large differences between the use of and preference for different contraceptive methods in the postpartum period in two communities in Texas. Surprisingly, despite substantial differences between Austin and El Paso, we found little difference between them in either use or preferences both before and after adjusting for sociodemographic covariates. In both cities, many more women had a preference for both LARC and permanent methods than were actually using these methods six-months after delivery. When restricting preferences to those elicited by way of a direct question regarding the method the respondent would like to be using three months in the future, the proportion preferring LARC was about twice as large as the proportion actually using such a method in both cities. After expanding the construction of preferences to include additional prompts, latent interest in both methods was found to increase further to the point that about 75% of the participants in each city were interested in using a highly effective method of contraception.

There were several methodological challenges that we confronted in designing the instruments for this study, and in constructing our measure of latent preferences since previous researchers have not used such questions and measures. To allow for the possibility that women's answers to the initial question regarding their preferred method would be constrained by cost or other barriers, and to accommodate the full range of definitions of birth control, we included a set of follow-up probe questions to further ascertain contraceptive desires. It is possible that this sequence of prompts may have led to response bias suggesting that we were not satisfied with the answer already given to the direct question, and were trying to elicit a preference for LAPM. However, we do have a previous experience in El Paso with the question about whether the respondent would have

liked to have been sterilized at the time of her last delivery, and found that responses had a very high correspondence with answers given in a more detailed interviewed conducted a year or two later.(9) The queries regarding interest in an IUD or an implant if it was offered for free or for a small fee are possibly more suggestive, but they do directly address the key question posed by the CHOICE project,(4, 5, 17) and other initiatives to offer LARC at no cost (REFS?).

Even with these caveats, the results constitute forceful evidence that the demand for highly effective contraception is not being met in these two settings. The number of women who answered the direct question saying that they would like to be using a LARC method greatly exceeds the number actually doing so, and a proven question about the demand for postpartum sterilization revealed a sizeable frustrated demand for that procedure. Moreover, the multivariable regression analyses of a preference for LARC or LAPM revealed that preference for these methods was not confined to particular segments of the population. Among participants who wanted to or might have an additional child, we found that Hispanics had a higher interest in LARC than other groups, and women over 30 who likely did not want to wait much more than two years before their next pregnancy were less likely to have an interest in LARC, but income, education, age, parity, and city were not significant predictors. Among women wanting no more children, the only significant predictor of a latent preference for LAPM were age and income, with a greater proportion of women over 30 having an interest in a highly effective method, and women with high incomes having less interest in these methods.

In contrast, the multivariable regression analyses of the odds of actually using LARC or LAPM in these two groups did indicate that advantaged groups were more likely than others to have realized their preference. In the model of LARC use among spacers who preferred

LARC, higher education, having insurance and household income were all associated with greater use. Indeed, after adjusting for other covariates, the estimated odds of a woman with an annual household income of \$75,000 or more using LARC were nearly eleven times those of a woman in a household with an annual income of less than \$10,000. In the model of use of LAPM among women preferring these methods who do not want additional children, insurance status was again significantly associated with use of a highly effective method.

The inability of low-income, uninsured women and couples to obtain or use LARC and permanent methods in this time frame is clearly consistent with the reports we have collected from family planning clinic leaders in Texas regarding the impact of the 2011 funding cuts on their ability to provide these methods to this population.(14) However, our data only refer to the period after the cuts, and do not speak to the change in the availability of long-acting and permanent methods that they likely precipitated. The lack of access we observed is likely also related to other barriers limiting the provision of LARC and male and female sterilization including lack of provider training, misperceptions regarding eligibility, safety and effectiveness, insufficient counseling, and structural barriers related to the postpartum provision of both LARC and female sterilization.(18-20)

Even without being able to fully account for the factors that have led to the situation we observed in these two Texas communities, the extent of the differences between preferences and use indicates the tremendous potential of improved policy to increase utilization of highly effective contraception in the postpartum period in Texas. Certainly one of the most promising policy improvements is to facilitate the provision of postpartum LARC through a specific funding mechanism for women with public insurance such as now exists in Colorado, South Carolina and New Mexico. Restoring the public funding for family planning that was cut so deeply by the Texas state legislature in 2011 is another critical step.

However, one of the key programs funded in the 2013 legislative session with the aim of closing this gap, the *Extended Primary Health Care Program*, will rely heavily on Federally Qualified Health Centers many of which do not have much experience providing long-acting or permanent methods.

While this study was conducted in a particular context, the question it addresses is a general one: Are women obtaining the contraceptive method they would like to be using on a timely basis in the postpartum period? Perhaps the most important lesson to be learned from our work is that much can be learned about the answer to this question by addressing it to patients directly and repeatedly as they pass through this critical stage.

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Table 1. Characteristics of Study Participants at Baseline, by City

Characteristics	Austin El Paso		Total	P
Characteristic	(n = 403)	(n = 400)	(n = 803)	
Age				
18 - 19	128 (31.8)	139 (34.8)	267 (33.3)	
20 - 24	120 (29.8)	109 (27.3)	229 (28.5)	0.34
25 - 29	96 (23.8)	81 (20.3)	177 (22.0)	
35 - 39	59 (14.6)	71 (17.8)	130 (16.2)	
Parity				
One	119 (29.5)	130 (32.5)	249 (31.0)	
Two	123 (30.5)	125 (31.3)	248 (30.9)	0.52
Three or more	161 (40.0)	145 (36.3)	306 (38.1)	
Childbearing Intentions				
Want more children	356 (46.8)	171 (42.4)	356 (44.3)	
Want no more children	376 (44.3)	192 (47.6)	376 (46.8)	0.40
Don't know	71 (8.8)	40 (9.9)	71 (8.8)	
Childbearing Intentions at 6 months ^a				
Want more children	172 (52.9)	161 (56.5)	333 (54.6)	
Want no more children	101 (31.1)	110 (38.6)	211 (34.6)	0.00
Don't know	52 (16.0)	14 (4.9)	66 (10.8)	
Relationship status				
Single	65 (16.2)	90 (22.5)	155 (19.3)	
Cohabiting	130 (32.3)	114 (28.5)	244 (30.4)	
Married	202 (50.3)	189 (47.3)	391 (48.8)	0.11
Separated/Divorce	3 (0.8)	7 (1.8)	10 (1.3)	
No Response	3 (0.7)	0 (0.0)	3 (0.30)	
Ethnicity				
Hispanic	253 (62.8)	362 (90.5)	615 (76.6)	
White	93 (23.1)	26 (6.5)	119 (14.8)	0.00
Black	39 (9.7)	7 (1.8)	46 (5.7)	
Other	18 (4.5)	5 (1.3)	23 (2.9)	
Education		(= 0 = 0	()	
Less than High School	149 (37.0)	113 (28.3)	262 (32.7)	0.00
High School	111 (27.5)	101 (25.3)	212 (26.4)	0.00
More than High School	143 (35.5)	186 (46.5)	329 (40.9)	
Insurance status	202 (74.0)	200 (55.0)	200 (75.0)	0.00
Public	302 (74.9)	300 (75.0)	300 (75.0)	0.98
Private	101 (25.1)	100 (25.0)	100 (25.0)	
Lost insurance by 6 months ^b	106 (40.0)	107 (57 0)	272 (52 6)	0.02
Yes	186 (48.8)	187 (57.0)	373 (52.6)	0.03
No	195 (51.2)	141 (43.0)	336 (47.4)	
Annual household income	02 (24.0)	171 (42.0)	264 (22.0)	
Less than 10,000	93 (24.0)	171 (42.8)	264 (32.9)	
10,000 - 19,999	105 (26.1)	92 (23.0)	197 (24.5)	0.00
20,000 - 34,999	75 (18.6)	47 (11.8)	122 (15.2)	0.00

35,000 - 74,999	56 (13.9)	56 (14.0)	112 (13.9)	
75,000 or more	60 (14.9)	34 (8.5)	94 (11.7)	
No Response	14 (3.5)	0(0.0)	14 (1.7)	

Percentages in parentheses

^an = 610 and includes all women except those who had been sterilized or who were using vasectomy as their method of contraception (Austin: n=325, El Paso: n=285) $^b n=709$ (Austin: n=381, El Paso: n=328)

100% 90% 80% Method Type 70% Don't know/no method 60% Less effective methods 50% Percentage of 40% Hormonal Sample 30% LARC 20% Sterilization 10% 0% 3 months 6 months 9 months Baseline **Survey Timepoint**

Figure 1. Current contraceptive method use at various durations postpartum

First three bars include all women present in the sample at 6 months and not pregnant (n=697). Fourth bar includes all women present in the sample at 9 months (n=645)

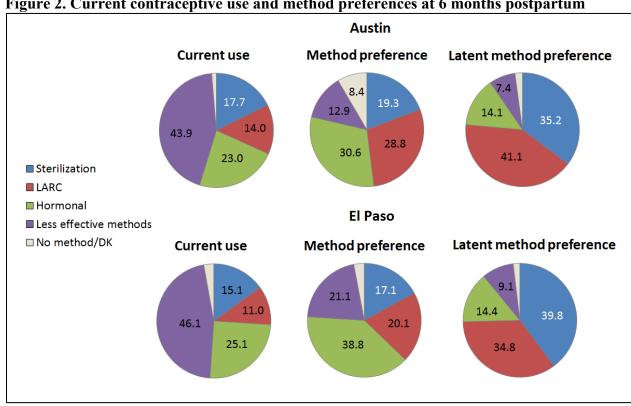


Figure 2. Current contraceptive use and method preferences at 6 months postpartum

Distribution of current method use by city: Pearson χ^2 (4, n=697) = 4.45, p= 0.35 Distribution of method preference by city: Pearson $\chi 2$ (4, n=697) = 24.05, p= 0.00 Distribution of latent method preference by city: Pearson $\chi 2$ (4, n=697) = 3.41, p= 0.49

Table 2. Logistic regression models predicting preference for LARC, and use of LARC given preference, among women who want more children or who don't know if they want more children

		Preference for LARC (n= 389)		Use of LARC Given Preference (n=217)	
	Odds Ratio	95% C.I.	Odds Ratio	95% C.I.	
City					
Austin	ref	ref	ref	ref	
El Paso	0.66	0.39-1.09	1.08	0.50-2.33	
Age					
18 - 24	ref	ref	ref	ref	
25 - 29	0.80	0.46-1.37	0.43 [†]	0.19-1.00	
30+	0.33***	0.18-0.63	0.24*	0.08-0.80	
Parity					
1	ref	ref	ref	ref	
2	1.07	0.65-1.76	0.91	0.42-1.95	
3+	1.34	0.71-2.54	2.03	0.80-5.16	
Education					
<high school<="" td=""><td>ref</td><td>ref</td><td>ref</td><td>ref</td></high>	ref	ref	ref	ref	
High School	0.91	0.48-1.72	1.84	0.69-4.92	
>High School	0.80	0.40-1.59	3.26*	1.11-9.60	
Insurance Status					
Retained Insurance	ref	ref	ref	ref	
Lost Insurance	0.71	0.42-1.18	0.40*	0.19-0.84	
Relationship Status					
Married	ref	ref	ref	ref	
Cohabiting	1.35	0.78-2.32	1.56	0.68-3.58	
Single	1.22	0.63-2.36	1.81	0.65-5.03	
Ethnicity					
Non-Hispanic	ref	ref	ref	ref	
Hispanic	2.10*	1.15-3.87	3.02*	1.04-8.82	
Annual Family Income					
<10,000	ref	ref	ref	ref	
10,000-19,999	1.57	0.84-2.93	1.31	0.53-3.22	
20,000-34,999	0.90	0.42-1.93	3.34*	1.03-10.85	
35,000-74,999	1.20	0.54-2.65	1.67	0.51-5.48	
75,000 or more	1.18	0.45-3.13	10.78**	2.11-55.13	

^{***} *p* < 0.001, ** *p* < 0.01, * *p* < 0.05, † *p* < 0.10

Table 3. Logistic regression models predicting preference for LAPM, and use of LAPM given preference, among women who want no more children or are sterilized

	Preference for LAPM (n= 306)		Use of LAPM Given Preference (n=276)	
	Odds Ratio	95% C.I.	Odds Ratio	95% C.I.
City				
Austin	ref	ref	ref	ref
El Paso	0.42	0.15-1.21	0.60^{\dagger}	0.33-1.05
Age				
18 - 24	ref	ref	ref	ref
25 - 29	2.21	0.61-7.97	0.69	0.28-1.69
30+	3.89*	1.08-13.93	1.52	0.65-3.53
Parity				
1	ref	ref	ref	ref
2	2.77	0.64-12.02	1.37	0.34-5.49
3+	3.35	0.78-14.43	3.92^{\dagger}	0.99-15.55
Education				
<high school<="" td=""><td>ref</td><td>ref</td><td>ref</td><td>ref</td></high>	ref	ref	ref	ref
High School	1.57	0.38-6.43	1.02	0.51-2.04
>High School	1.72	0.40-7.29	1.87	0.84-4.17
Insurance Status				
Retained Insurance	ref	ref	ref	ref
Lost Insurance	1.18	0.39-3.62	0.33**	0.18-0.63
Relationship Status				
Married	ref	ref	ref	ref
Cohabiting	1.14	0.32-4.07	1.07	0.56-2.06
Single	0.85	0.18-4.05	1.05	0.47-2.38
Ethnicity				
Non-Hispanic	ref	ref	ref	ref
Hispanic	1.93	0.58-6.43	0.71	0.31-1.64
Annual Family Income				
<10,000	ref	ref	ref	ref
10,000-19,999	0.40	0.08-1.86	1.49	0.70-3.17
20,000-34,999	0.33	0.06-1.88	1.07	0.48-2.37
35,000-74,999	0.13*	0.02-0.87	1.07	0.39-2.93
75,000 or more	0.21	0.02-2.14	0.29^{\dagger}	0.08-1.00

^{**} p < 0.01, * p < 0.05, † p < 0.10