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Adherence to Zidovudine for the Prevention of Perinatal Transmission in HIV-Infected Pregnant Women: The Impact of Social Network Factors, Side Effects, and Perceived Treatment Efficacy

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Abstract

Adherence to zidovudine (ZDV) prophylaxis among 78 pregnant HIV-infected women was measured with 2 physiologic markers. Long-term adherence was measured with blood assays for macrocytosis, a clinical indicator of ZDV use; 53 women (67.9%) were adherent. Short-term adherence was measured with urine assays for ZDV; 48 women (61.5%) were adherent. Comparison of urine assay and interview data indicated that 29% had not taken the last dose that they reported. Participation in HIV support groups and disclosure to the participant's mother were associated with better adherence. These social network factors may enable HIV-infected pregnant women to cope more effectively with the multiple stressors they face and facilitate prenatal care.

Keywords

HIV; women; adherence

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Introduction

In 1994 the AIDS Clinical Trial Group (ACTG) Protocol 076 reported that 8% of infants born to asymptomatic HIV-infected pregnant women on a three-part regimen of zidovudine (ZDV) were HIV-infected compared with 26% for the control group, amounting to a 68% reduction in vertical transmission (CDC, Centers for Disease Control and Prevention, 1994). The trial regimen consisted of oral antepartum ZDV, intravenous intrapartum ZDV, and oral ZDV for the newborn for six weeks. Shortly thereafter, the U.S. Public Health Service recommended HIV counseling and voluntary testing of all pregnant women (CDC, 1995) and prophylactic treatment of all infected women and their infants according to the trial regimen (CDC, 1994). Implementation of these recommendations into clinical community practice occurred rapidly. Use of ZDV by infected pregnant women increased from 22% to 89% and transmission rates decreased from 19% to 8% for infants delivered after March 1,1994 followed in an observational natural history study (Cooper et al., 1996). Wiznia et al. (1996) reported a 75% acceptance rate for women enrolled in prenatal care at a community-based urban medical center.

Acceptance of a prescription, however, does not guarantee adherence with the regimen. Two-thirds of women who accepted treatment were considered adherent according to chart review of completion of treatment (Wiznia et al., 1996); non-completion was associated with cocaine use during pregnancy. Only 34.2% of women prescribed ZDV prophylaxis during the last 2 trimesters were adherent according to a large-scale pharmacy claims-based analysis (Laine et al., 2000). Adherence was defined as having sufficient medication to cover at least 80% of days from the first prescription until delivery according to paid pharmacy claims. Poor adherence was associated with Hispanic and Black race and age < 20 years. A majority of women (80%) participatingin the Perinatal Guidelines Evaluation Project (PGEP)–a large, multisite study funded by the CDC in 5 states–reported missing no ZDV doses in the 4 days prior to interview (Wilson et al., 2001); missing ZDV doses was associated with self-reported prenatal drug use (heroin, cocaine) and missing prenatal vitamins. A subset of PGEP women (n = 53) were also assessed with electronic monitors, the Medication Event Monitoring System (MEMS) (Ickovics et al., 2004). In contrast to self-report, the mean rate of adherence (% of prescribed doses taken) for the three weeks prior to delivery was only 50%.

The goals of the current study were to expand the current body of research on adherence to prenatal ZDV prophylaxis by assessing adherence with physiologic markers and to examine the association of these adherence outcomes with psychosocial, clinical, and sociodemographic factors. Two physiological indices, urine assay and mean corpuscular volume (MCV) of erythrocytes, were employed. Urine levels of ZDV and its metabolite, glucoronide ZDV (GZDV), can only be used as an index of short-term adherence because of ZDV's short half-life of 1.3 hours (O'Sullivan et al., 1993). This allows, however, for comparison between the objective measure of urine levels and self-report for the most recent dose taken. Long-term adherence to ZDV has been assessed with MCV in prior studies (Duong et al., 2001; Ferrando, Wall, Batki, & Sorensen, 1996; Romanelli, Empey, & Pomeroy, 2002; Samet et al., 1992) because macrocytosis is a common side effect of

sustained ZDV use and results in elevated MCV levels (Hambleton, 1997); significant increases occur within two weeks of treatment onset (Richman, Fischl, & Grieco, 1987).

We addressed social network and medication-related psychosocial factors (severity of side effects and efficacy beliefs) as areas likely to be related to adherence with ZDV prophylaxis. In studies of non-pregnant samples, belief in ZDV efficacy was associated with greater adherence (Samet et al., 1992) and long-term use (Smith, Rapkin, Morrison, & Kammerman, 1997); problems with side effects were associated with lower adherence (Catz, Kelly, Bogart, Benotsch, & McAuliffe, 2000) and termination of treatment (Smith et al., 1997).

Social network factors of disclosure of HIV serostatus and social support were examined because they appear to be especially relevant to adjustment to living with HIV infection for infected women. Satisfaction with support was found to mediate the relationship between adaptive coping and psychological distress in a sample of Hispanic and African-American women (Simoni, Demas, Mason, Drossman, & Davis, 2000). Disclosure has been related to the availability (Moneyham et al., 1996) and frequency (Simoni et al., 2000) of social support in samples of seropositive women and to adherence among samples of infected mothers for their own treatment (Mellins et al., 2002) and for postnatal prophylaxis of the exposed infant (Demas et al., 2002).

Materials and Methods

Procedures

The sample was comprised of 78 HIV-infected pregnant women who were a subset of a study population enrolled in a longitudinal study of vertical transmission of HIV, the New York City Perinatal HIV Transmission Collaborative Study. This study is part of a multi-center study sponsored by the CDC since 1985, the Perinatal AIDS Collaborative Transmission Studies (PACTS), described elsewhere (Thomas et al., 1994). PACTS participants are likely to be highly representative of the target population of HIV-infected pregnant women because over 95% of HIV-infected women who deliver at the New York City sites were enrolled in PACTS. Inclusion criteria for this sub-study of adherence to ZDV prophylaxis were: pregnancy of at least 20 gestational weeks, fluency in English or Spanish, and signed written informed consent. During the study period from April 1997 through June 1998, 90 of 109 pregnant PACTS participants in three New York sites were eligible for the present adherence study and 86 (95.6%) agreed to participate and were enrolled.

Seven of these women were excluded from the current analysis because they did not take ZDV during the index pregnancy, and one because MCV data was incomplete and a urine sample was not collected. These 8 women did not vary significantly for age, race, ethnicity, and substance abuse compared with the 78 women included in the final data set. Of the 7 women who did not take ZDV during the index pregnancy, four had taken ZDV previously when not pregnant; they were offered the prenatal prophylaxis and had refused treatment due to concerns regarding side effects or potential harm to the infant. Five of the 7 women reported that they had been counseled by their care providers regarding the post-natal six-

week prophylactic regimen of oral ZDV for newborns and 6 said they planned to administer the treatment to their infants.

The final data set for analysis of long-term and short-term adherence thus consisted of 78 women; we did not find statistically significant differences between these 78 women and other PACTS participants who were not included in this substudy when age, race, ethnicity and substance abuse were examined. Comparison of urine assay analysis (n = 73) with self-report did not include 5 women who reported that they had not taken ZDV in the prior 24 hours.

The study was conducted from April 1997 through June 1998 at three PACTS sites in New York City: Bronx-Lebanon, Montefiore, and Metropolitan Hospital Centers. Approval was obtained from the institutional review boards affiliated with the three sites and with the Medical and Health Research Association of New York City, Inc., the grantee agency. Participants were paid US$50. Standardized interviews, described below, were administered by trained staff members to collect social network data and ZDV-specific utilization patterns, severity of side effects, and perceptions of efficacy. The interview was translated into Spanish and checked with back-translation; it was administered in Spanish to 5 (6.5%) participants. Blood and urine samples were collected at interview to conduct assays for physiological markers of adherence as described below.

Measures of Adherence

Urine Assay Procedures: Observed ZDV Levels—Urine samples were collected from the 73 participants who reported taking any ZDV within the 24 hours prior to interview and were frozen at −70° within 70 minutes of collection and sent for analysis to the Antiviral Assay Laboratory, Division of Infectious Diseases, Department of Pediatrics, University of California at San Diego. Observed ZDV level was calculated as the product of observed ZDV urine concentration and urine volume. A simple reversed-phase high pressure liquid chromatography (HPLC) method was used for the simultaneous determination of ZDV and its glucoronide metabolite (GZDV) (Holland, Godredsen, & Connor, 1998). The intraassay and between-assay means for precision and accuracy for both ZDV and GZDV are 7.8% CV and 4.3% deviation; the sensitivity of the method is 5μg/ml. Reliability of this method was further indicated by the lack of cross-reactions with blank pregnant urine, HIV medications, and other drugs.

Comparison of Self-Report for Last Dose with Observed Urine Levels of ZDV —Due to the short half-life of ZDV, only the most recent dose at time of interview could be adequately assessed for comparison purposes. Participants were queried as to the time and size of the last dose they had taken at the time of collection of urine samples. To compare self-reported adherence with the urine assay, we calculated what percentage of the *expected* level of ZDV (based on the last dose reported by the participant) was actually found in the urine sample, i.e., the *observed* level (Observed/Expected × 100). Higher percentages indicate that participants had taken larger proportions of the last dose they reported.

The expected ZDV level was determined by using a biexponential model (Gilbaldi & Perrier, 1975) to estimate plasma concentrations as a function of time and size of last dose

reported by participants and body weight reported by clinicians. Model parameters included: ZDV half-life of 1.3 hours (O'Sullivan et al., 1993), absorption rate constant of 2 hours^{-1}, extent of entering plasma and 70% absorption fraction (E. Capperelli, personal communication). The concentration function was integrated over time to estimate total ZDV plasma accretion between the time of sample collection and time of prior void. From this value, expected ZDV urine level was calculated assuming 30% renal clearance of total body clearance of 26 ml min^{-1} kg^{-1} (O'Sullivan et al., 1993).

Long-Term Adherence: Mean Corpuscular Volume (MCV) of Erythrocytes— MCVs over 95 fl have been reported in 94% of patients taking ZDV in a clinical trial compared with 9% of those on placebo (Lim & Volberding, 1994). Prior studies have defined adherence as MCV ≥ 100 fl (Ferrando et al., 1996) and ≥ 95 fl (Samet et al., 1992). In the current study, participants were considered to demonstrate long-term adherence if MCV ≥ 95 fl and ZDV had been taken for at least one month. MCV was determined within 6 hours of collection by standard Coulter flow cytometry with the S-Plus Hematology Analyzer at the New York City Department of Health laboratories, the usual site for such tests for PACTS-New York City.

MCV levels may be inflated by vitamin B_{12} and folate deficiencies (Richman et al., 1987), smoking and alcoholism (Power, Holzman, & Schulkin, 2000). Our ability to control for such potentially confounding variables was somewhat limited because baseline MCV levels prior to onset of ZDV prophylaxis were not available for comparison, and folate and B_{12} levels were not evaluated by PACTS or this study. Self-report data on smoking and alcohol use during pregnancy were collected by PACTS, and no statistical relationship to MCV levels was found.

Medication-Related Variables

Severity of Side Effects—Five ZDV side effects reported in the literature (nausea, headaches, fatigue, nervousness, anemia) (Richman et al., 1987) and two determined in a preliminary open-ended survey of 40 HIV-infected pregnant and post-partum women (hair loss/thinning, skin or nails spotted/darkened) were rated on an 8-point scale for severity, where 1 = *didn't bother you at all* and 8 = *botheredyou a lot*. Participants were instructed to rate each item specifically for ZDV treatment and not to include the effects of pregnancy in their replies. The items were summed to create a severity of side effects scale with satisfactory internal consistency (Cronbach's α = .72).

Perceived General Efficacy of ZDV—Two items assessing efficacy of ZDV treatment ("AZT helps people live longer" and "AZT helps people stay healthier") were rated on an 8-point scale, where 1 = *disagree a lot* and 8 = *agree a lot*. Responses were summed to produce a general efficacy scale with fair internal consistency (Cronbach's α = .69). The higher the score the greater the rating of perceived efficacy.

Perceived Efficacy of Prophylaxis for Perinatal Transmission—Participants rated the probability (0 to 100%) of an infant becoming infected in two situations: if a mother took ZDV during pregnancy and if a mother did not. A score was created by calculating the

difference between the two probabilities (Untreated minus Treated) which represented the degree to which the prophylaxis reduced the probability of perinatal transmission. Higher scores indicated greater probability that the prophylaxis reduced infant infection and hence greater perceived efficacy.

Social Network Assessment

Participation in religious activities and HIV support groups and disclosure of HIV status to parents and partners were assessed with items adapted from the Social Network Index (Cohen, Doyle, Skoner, Rabin, & Gwaltney, 1997). Perceived availability of social support was assessed with an 8-item scale to determine the probability that they could depend on others for emotional, financial, and instrumental support. This scale was originally developed with seven items for a study of gay and bisexual men either at-risk for HIV or identified as HIV-infected (Cronbach's α = .87) (O'Brien, Wortman, Kessler, & Joseph, 1998). It has been used successfully in a large cohort study (N = 319) of HIV-infected pregnant women (Cronbach's α = .85) with the addition of an item to determine whether child care would be available if the respondent were ill (Ickovics et al., 2000). The response scale ranged from 1 (*definitely not*) to 5 (*definitely yes*) (Cronbach's α for the current study = .87).

Statistical Analysis

Demographic, clinical, and substance abuse variables were obtained from the NYC PACTS database. AIDS disease status was defined according to the classification criteria of the CDC (1992). Symptomatic status was assigned for histories of constitutional symptoms (e.g., fever, weight loss) or infectious disease (e.g., tuberculosis, oral thrush). Bivariate analyses were conducted with Fisher's Exact Test, t-tests, with non-parametric tests used as appropriate, to determine if demographic and clinical variables, medication-related, or social network factors were associated with long- and short-term adherence outcomes. Based on the bivariate results, multivariate logistic regressions were performed to determine which study variables were associated with long- and short-term adherence outcomes. Variables associated with adherence in the bivariate analyses at p <.10 were included for testing in the multivariate models. The significance level for all other analyses was a two-tailed α = .05. The Statistical Package for the Social Sciences (SPSS, Inc., Chicago, Illinois, USA) was used for all analyses.

Results

Participant Characteristics

Fifty-three percent of the participants were Black and 41% Hispanic. A history of substance abuse was reported by 49% who had ever used one or more hard drugs (cocaine, heroin, or illicit methadone) through injection, snorting, smoking or other methods and by 17% during pregnancy. Six women (8%) reported a history of injection drug use. One-third (30%) had AIDS and 34% had CD4 counts < 500 cells mm^{-3} (Table 1).

Rates of Adherence

Comparison of Urine Assay Data with Self-Report—Urine assay data for ZDV and its metabolite, GZDV, were compared with self-report data for the most recent dose taken at time of urine sample collection for the 73 participants who reported taking ZDV within the prior 24 hours. Of these, almost one-third (29%) had no observable levels (i.e., < 5 μg) and were considered to have taken none of the last dose that they reported. Only 12% had taken at least 50% of the ZDV that they reported, and 59% had taken part of the reported dose but < 50%.

Short-Term Adherence—The urine assay data were dichotomized into categories of short-term adherence to simplify quantitative analyses. Sixty-two percent had taken at least partial doses according to urine assay analysis and were classified as adherent. Participants who had no observable levels (i.e., < 5 μg) of both ZDV and its metabolite, GZDV, were considered non-adherent, as were 5 women who reported taking no dose within 24 hours and thus did not have a urine assay.

Long-Term Adherence—Nearly one-third (32%) were non-adherent according to our definition of long-term adherence, i.e., MCV level < 95 fl.

Consistency Between Physiologic Measures of Adherence—Most participants were consistently adherent or non-adherent according to the physiologic ratings. Thirty-eight (49%) were adherent and 19% were non-adherent on both indices. The remainder were discordant: Ten (13%) were adherent short-term but not long-term, and 15 (19%) were adherent long-term but not short-term.

Medication-Related Variables

Side Effects—The most common side effect attributed to ZDV use was headache, reported by 58%, compared with hair loss/thinning (14%) to fatigue and nervousness, both reported by 31%. Moderate-high levels of severity were most often reported for headaches (20%) and nervousness (19%).

Perceived General Efficacy of ZDV—A majority agreed that ZDV prolongs life (77%) and maintains health (80%); 40% and 56%, respectively, rated these two items at the upper quarter of the response scale, indicating high perceived efficacy.

Perceived Efficacy of Prophylaxis for Perinatal Transmission—The probability of HIV infection for an infant born to an untreated woman was rated as high (median = 75%) and significantly lower (median = 25%) if the mother did take ZDV (Wilcoxon Signed Ranks Test, Z = −7. 118, $p < .001$).

Social Network Factors

Over half (55%) of study participants reported that their mothers knew of their serostatus. The rate of disclosure to fathers was lower (27%), and limited to cases in which the participants had also disclosed to their mothers. A higher proportion reported that their current partner knew their serostatus (86%). Fourteen women said they had no current

partner, and three women reported that their current partner was not the father of the baby. More than a third participated in church or religious activities (36%), and 23% in HIV support groups.

Factors Associated with Long-Term and Short-Term Adherence

Demographic and clinical factors, such as HIV disease status, were not significantly related to either short-term or long-term adherence. Side effect severity and perceived efficacy–both generally and specific to the prophylaxis–were also unrelated to adherence behaviors. In bivariate analyses, disclosure of HIV status to mothers ($p = .032$), participation in an HIV support group ($p = .007$), and greater gestational age ($p = .021$) were associated with short-term adherence. In multivariate analyses, only HIV support group participation (odds ratio [OR] = 6.35) retained significance in the logistic regression model ($\chi^2(3, N = 78) = 14.96$ $p = .002$) for short-term adherence. In bivariate analyses of long-term adherence, disclosure to mothers ($p = .028$) and greater perceived availability of social support (Mann-Whitney U = 806.5, $p = .021$) showed significant associations; disclosure to partners was marginally related ($p < .10$). Only disclosure to mothers remained significant (OR = 2.965) in the logistic regression model, $\chi^2(3, N = 78) = 8.245$, $p = .041$. Multivariate analyses are summarized in Table 2.

Because of their statistical association with adherence, we then compared the social network factors (social support, disclosure and support group participation) with key demographic (e.g., age, race, ethnicity, substance abuse) and clinical variables (e.g., HIV illness markers). No statistically significant associations were found, except that women who participated in HIV support groups were more advanced in their pregnancies (gestational age = 30.2 weeks) than those who did not participate (gestational age = 26.3 weeks; (Mann-Whitney U = 332.0, $p = .014$).

Discussion

In our cohort of urban, HIV-infected pregnant women, we examined adherence to zidovudine (ZDV) prophylaxis with two physiologic measures and the relationship of these outcomes with treatment side effects, perceived efficacy, and clinical, sociodemographic, and social network factors. In our sample, medication-related variables of side effect severity and perceived efficacy were not associated with adherence, a finding discrepant with other studies of non-pregnant adults (Catz et al., 2000; Samet et al., 1992; Smith et al., 1997). Our negative finding for side effects may in part be explained by the nature of pregnancy as a well-defined temporary period driven by the high reward of a healthy infant, which may facilitate greater toleration of side effects. We believe our negative findings for perceptions of ZDV treatment are consistent with those of Wilson et al. (2001) from a 4-state study of 247 HIV-infected pregnant women taking ZDV. The authors similarly reported the absence of significant associations between adherence and ZDV-specific factors, including perceptions of treatment efficacy, leading them to posit that " … situational factors, rather than those specifically related to zidovudine, are the primary factors associated with adherence during the prenatal period" (page 1239).

Pregnancy status may also have an impact on the reliability of self-reported data. Overestimation of self-reported adherence in non-pregnant, non-HIV infected samples is common (Gordis, Markowitz, & Lilienfeld, 1969), and thus the low rates of adherence based on physiological markers (62-68%) found in our study are not surprising. Nonetheless, the disparity we found between self-report of last dose and the results of the urine analysis was strikingly large: 29% had taken none of the last dose reported and only 12% had taken at least 50% of that dose. Such discrepancies suggest that pregnant women may find it especially difficult to admit that they have been inconsistent in taking medication they believe can help their unborn child. Also, the social undesirability of substance abuse and alcohol use during pregnancy–in addition to guilt or embarrassment–may cause these woman to be more likely to deny or under report such behaviors and may in part explain why 13% of the sample refused to answer such questions.

In our sample, participation in HIV support groups and disclosure to mothers were variables associated with short-term and long-term adherence outcomes, respectively, in multivariate analyses. These factors may enable pregnant women to cope more effectively with the multiple stressors faced by women with HIV infection, including stigma and social isolation (Ickovics et al., 2000). In addition, support provided by a woman's social network may function as a major coping resource during pregnancy to alleviate stress and facilitate access to prenatal care (Dunkel-Schetter, Gurung, Lobel, & Wadhwa, 2004). Relatively little research has been published on factors associated with adherence among HIV-infected pregnant women for comparison, but our findings are consistent with prior studies which report that social support, especially from family members, has a positive influence on adherence with HIV treatment regimens (Catz et al., 2000).

Fortunately, only one of the 78 infants born to women in our sample was infected; this prevents us from being able to conduct statistical analysis of the relationship between indices of maternal adherence and transmission to the infant. Strict adherence is necessary, nonetheless, to prevent the development of drug resistance and optimize maternal health according to the recent guidelines on use of antiretroviral drugs in pregnant infected women (CDC, 2002).

One of the landmark advances in HIV treatment is combination therapy, frequently consisting of three medications including highly effective protease inhibitors, a regimen which has been associated with lower rates of transmission compared with the ZDV monotherapy prescribed to our sample (Cooper et al., 2002). Outside of Europe and the United States, however, with limited resources to deliver health services, ZDV alone or in combination with lamivudine are still recommended as feasible, safe and effective alternatives (WHO, 2004). We believe the findings of this study thus remain applicable to the evolving strategies for the prevention of HIV transmission to infants among pregnant HIV-infected women.

Although we attempted to be comprehensive in our assessment of adherence behaviors by using a combination of self-report and physiologic markers, the applicability of our findings may be limited by small sample size, the cross-sectional design of the study, the potential bias of self-report for substance abuse, and the problematic nature of quantifying adherence

objectively. For example, alcohol and tobacco use during pregnancy, which can inflate MCV levels, were assessed by self-report and may be especially vulnerable to bias as they are not considered socially desirable activities during pregnancy. Folate and vitamin B_{12} deficiencies may also result in macrocytosis or elevated MCVs and were not evaluated by this study. However, all study participants were engaged in ongoing prenatal care, which reduces the likelihood of macro-cytosis due to untreated anemia (Power, Holzman, & Schulkin 2000). Thus, while the physiologic markers of MCV and urine assay have shortcomings as precise indices of ZDV adherence, we believe that they provided satisfactory and objective appraisals of long- and short-term adherence behaviors, respectively, for this study. Despite limitations, we believe our findings suggest that future research among HIV-infected pregnant women should not rely upon self-report adherence data and should include physiologic or other more objective means of data collection such as electronic monitoring devices.

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Table 1

Participant Characteristics (*N* = 78)

	N	%
Race		
Black	41	53
Hispanic	32	41
White/Other	5	6
Means of Contracting HIV Infection		
Injecting Drug Use	1	1
Heterosexual Contact	65	83
Both	5	7
Other	2	3
Unknown	5	6
Substance Abuse		
History	37	49
During Pregnancy		
Yes	13	17
No	55	70
Refused to answer [a]	10	13
Alcohol Use During Pregnancy	6	8
Tobacco Smoking During Pregnancy	32	43
CD4 Cell Counts[b]		
< 500 cells mm^{-3}	25	34
≥ 500 cells mm^{-3}	49	66
HIV Illness Stage[b]		
Asymptomatic	39	51
Symptomatic	14	19
AIDS	23	30
Completed High School[b]	24	32
	Median	
Age, years	30	
Months since HIV Notification	22	
Prior pregnancies	4	
Prior live births	2	
Gestational age, weeks	27	

[a] Indicates participants who declined to answer items regarding use of cocaine, heroin, or illicit methadone during pregnancy.

[b] Due to missing data, *n* = 74-76.

Table 2

Multivariate Analyses: Logistic Regression

	Short-Term Adherence		
	Odds Ratio	**95% CI**	***p***
HIV Support Group	6.35	1.26-31.99	.025
Disclosed to Mother	2.44	0.866-6.86	.092
Gestational Age	1.09	0.999-1.20	.053
	Long-Term Adherence		
	Odds Ratio	95% CI	*p*
Perceived Social Support	1.08	1.00-1.18	.070
Disclosed to Mother	2.97	1.02-8.61	.046
Disclosed to Partner	0.19	0.22-2.20	.479