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Regional Differences in Time to Pregnancy Among Fertile Women from Five Colombian Regions with Different use of Glyphosate

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The objective of this study was to test whether there was an association between the use of glyphosate when applied by aerial spray for the eradication of illicit crops (cocaine and poppy) and time to pregnancy (TTP) among fertile women. A retrospective cohort study (with an ecological exposure index) of first pregnancies was undertaken in 2592 fertile Colombian women from 5 regions with different uses of glyphosate. Women were interviewed regarding potential reproductive, lifestyle, and work history predictors of TTP, which was measured in months. Fecundability odds ratios (fOR) were estimated using a discrete time analogue of Cox's proportional hazard model. There were differences in TTP between regions. In the final multivariate model, the main predictor was the region adjusted by irregular relationship with partner, maternal age at first pregnancy, and, marginally, coffee consumption and self-perception of water pollution. Boyacá, a region with traditional crops and. recently, illicit crops without glyphosate eradication spraying (manual eradication), displayed minimal risk and was the reference region. Other regions, including Sierra Nevada (control area, organic agriculture), Putumayo and Nariño (illicit crops and intensive eradication spray program), and Valle del Cauca, demonstrated greater risk of longer TTP, with the highest risk for Valle del Cauca (fOR 0.15, 95% CI 0.12, 0.18), a sugar-cane region with a history of use of glyphosate and others chemicals for more than 30 yr. The reduced fecundability in some regions was not associated with the use of glyphosate for eradication spraying. The observed ecological differences remain unexplained and may be produced by varying exposures to environmental factors, history of contraceptive programs in the region, or psychological distress. Future studies examining these or other possible causes are needed.

Glyphosate is one of the most widely used herbicides globally and has been registered for use in Colombia since 1972 for weed control in a wide range of crops and in the process of sugar cane maturation. Beginning in the early 1980s, it was used for eradicating the illegal crops of coca (*Erythroxylum coca*) and poppy (*Papaver sominferum*). Since 2000, it has been more widely used for the eradication of illicit crops. The area of coca sprayed with glyphosate has shown a steady increase over recent years, reaching 153,000 ha in 2007 (personal communication, National Police of Colombia, Bogotá, December 2007). According to Colombian use data, 10–13% of the total amount of glyphosate purchased in the country is used for aerial spraying of illicit crops; the remainder is used in both legal and illegal crop production (Solomon et al., 2007).

Colombia is organized into 32 administrative departments (*departmentos*). In 12 of them, illicit crops have been sprayed with glyphosate by aerial application since 2000. The location and amounts of glyphosate applied for this purpose are accurately

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known. Glyphosate is used for other purposes in all departments, but actual use statistics are not known as sales data are not collected.

In developed countries, investigators have increasingly used time to pregnancy (TTP) as a sensitive clinical marker of multiple early adverse reproductive effects (Baird et al., 1986; Joffe 1997, 2000; Joffe & Barnes 2000; Tingen et al., 2004; Joffe et al., 2005). Epidemiological studies examined the role of agriculture and pesticide exposure in reducing the probability of achieving conception in a menstrual cycle (also known as fecundability) with mixed results (De Cock et al., 1994; Larsen et al., 1998; Curtis et al., 1999; Thonneau et al., 1999; Abell et al., 2000; Petrelli & Figà-Talamanca, 2001; Sallmén et al., 2003; Idrovo et al., 2005; Bretveld et al., 2006; Lauria et al., 2006; Bretveld et al., 2008; Joffe et al., 2008).

There have been some reports in the literature of adverse reproductive outcomes associated with pesticide use, most of which are described in more detail in a recent review (Wigle et al., 2008). Arbuckle et al. (2001) observed a rise in the risk of early abortion when preconception self-reported exposures to phenoxyacetic acid herbicides were present (odds ratio [OR] = 1.5, $CI_{95\%}$ 1.1–2.1; positive effect if greater than 1) and for late abortions, self-reported preconception exposure to glyphosate (OR = 1.7, $CI_{95\%}$ 1–2.9) was associated with higher risks. In another study, Curtis et al. (1999) reported a positive association (decrease in fecundability of 20% or more) measured through the outcome, TTP, when both spouses reported exposure to pesticide activities, with 5 of 13 pesticides categories (dicamba, glyphosate, phenoxy herbicides, organophosphorus insecticides, and thiocarbamates). Garry et al. (2002), studying pesticide applicators in Minnesota through a cross-sectional study of 695 workers and 1532 children (offspring), observed that self-reported use of the herbicide glyphosate yielded an OR of 3.6 ($CI_{95\%}$ 1.3–9.6) in relation to attention deficit disorder/attention deficit-hyperactivity disorder (ADD/ADHD), and pointed out that herbicides applied in the spring might be a factor in the birth defects.

Our objective in the current study was to test for differences in TTP for first pregnancy among fertile women selected from five regions of Colombia with different use patterns of glyphosate. This study also took into account other known factors affecting fecundability. A priori, it was postulated that the use of glyphosate in aerial spraying programs for eradication of illicit crops might be associated with reduced fecundability, and, considering that there are no biomarkers for exposure to glyphosate, an ecological exposure index was chosen.

MATERIALS AND METHODS

Design and Population

Between August 2004 and February 2005, a cross-sectional study of first pregnancies was carried out among women based on residence in one of five different regions (departments) from Colombia (Figure 1). All participants were informed about the objectives of the study, and invited to participate if their first pregnancy occurred during the last 5 yr (since November 1999) and they did not use contraceptives during the year prior to becoming pregnant. The latter was to reduce reporting bias because there is no accurate method to adjust for the effect of the use of contraception on fecundity (Tingen et al., 2004). Only data on first pregnancies were used, to reduce recall bias and other potential biases that are associated with subsequent pregnancies. Only one pregnancy was used to maintain outcome independence and minimize the effect of previous reproductive history (Olsen & Skov, 1993).

Two days of training were carried out for interviewers and supervisors to explain the objectives of the project and the questionnaire to be applied. All interviewers lived in the study area and were supervised by local epidemiologists who knew the study area and who were well known to the population. In each area, studies started at the closest household where water and sediment samples were taken as part of the assessment of aerially applied glyphosate (Solomon et al., 2007). From the first household, the interview team moved away (centrifugally), visiting house by house to identify women who met the inclusion criteria until the sample size (600 women in each zone) was achieved. Because field workers were well known by the population, there were no refusals to enter the study, except in Valle del Cauca, where 3% of identified women declined to enter the study, mainly because their husbands did not allow them to participate. There were some differences among the five study sites that required us to visit more households in some areas than in others. For example, in Boyacá and Nariño, women start families at an early age; thus, when asked about first pregnancy in the last 5 yr there were many who were in the appropriate age group but had their first pregnancy more than 5 yr previously and therefore did not meet the inclusion criteria. In Valle del Cauca, most women had taken oral contraceptives in the last year, an exclusion criterion for the study. The population of Valle is different because it is a more developed department, was one of the first departments (if not the first) where extended family planning was initiated in the 1960s, and many villages (*veredas*) needed to be visited in order to obtain the sample size.

All women responding to the oral invitation were interviewed in their homes. Those who were confirmed as meeting the inclusion criteria were informed about the objectives of the study. Care was taken to ensure participants that there would be no reprisal for participation or nonparticipation, and that the investigators guaranteed the privacy of the information collected. Each participant provided written informed consent, in keeping with ethical approval by the Ethics Review Board of the Fundación Santa Fé de Bogotá, Colombia. Of a total of 3005 women interviewed, 233 women were excluded without TTP data and 21 with TTP values greater than 60 mo. Hence, 2751 (91.6%) were included in the analyses. However, for the

FIG. 1. Location of the study areas in Colombia (departments).

multiple regression and the alternative models, a restricted analysis was conducted without the 159 women who reported consultation with a physician because of fertility problems. This removed potential bias that may have been introduced by those who suspected themselves to be subfertile (Tingen et al., 2004; Idrovo et al., 2005; Joffe et al., 2005)

Exposure Assessment

As exposure could not be measured directly, an ecological design was used in which five different regions in the country, with different levels of exposure, were selected according to agricultural practices and presence or not of the aerial spray program for eradication of illicit crops with glyphosate. Table 1 shows the characteristics of the study areas.

Outcome Measurement

Valid data on TTP can be derived retrospectively, with a recall time of 14 yr or more (Joffe et al., 1995). A modified version of the key question from the questionnaire of Baird et al. (1986) was used to elicit TTP: "How many months were you having sexual intercourse before you became pregnant for the first time?" The questionnaire was field tested in the five different regions to ensure the question was clearly understood in all areas since the departments are far from each other and there are subtle differences in understanding some terms. TTP was defined as duration in months, not divided by menstrual cycle duration in days, because women are more able to recall time in months than in cycles (Joffe, 1997). In this case, months and cycles were treated as equivalents.

Potential Confounders

During the interview, participants also provided information on potential confounders, including age at which the woman started trying to become pregnant, age at first pregnancy, and current age; relationship with partner; work history and gynecologic and medical history prior to first pregnancy; x-ray exposure in the year prior to conception; body image perception prior to conception as a proxy for body mass index (Singh, 1994; Madrigal-Fritsch et al., 1999; Romieu et al., 2004); and lifestyle practices in the year prior to conception, such as

TABLE 1
Geographic, Population, Agriculture, and Pesticide Use Characteristics in the Study Regions

Department	Description of the study area	Most common crops	Usual level of pesticide use	Glyphosate aerial spray program
Boyacá	Boyacá is located 130 km northwest of Bogotá (Figure 1), and the west zone is at 850 m a.s.l. with an annual mean temperature of 24°C and rainfall of 2250 mm per year. Ten out of the 132 municipalities belong to this zone and 5 were selected for the study. Boyacá has 1,404,309 inhabitants, 36,136 of which reside in the municipalities selected. Thirty percent are women between 15 and 49 yr of age. The inhabitants of this department are mainly mestizos.	Vegetables, potato, maize, barley, sugar cane, wheat, plantain, and some fruits are the main crops in the area. Illicit crops have been grown since 1992	Herbicides, fungicides, insecticides, and rodenticides are used in the study area. Glyphosate is used as herbicide.	None (manual eradication of illicit crops)
Nariño	Tumaco (located in Nariño, Figure 1) is one of the largest municipalities in the country (3760 $km^{2)}$, located at 2 m a.s.l., has an annual mean temperature of 28ºC and rainfall of 2,531 mm. It is located at the southwest corner of the country and border Ecuador to the south. Forty-nine percent of the 162,606 inhabitants live in rural areas. The projected number of women in fertile age (15–49 yr) for 2004 was 36,386. The population of Tumaco is largely of African origin.	Agriculture makes up 80% of the economic activities of the population. Main crops are oil (African) palm, cacao, plantain, and coconut. Forestry is another important source of income, as well as fish and aquaculture. Illicit crops have been grown in the area during the last 10 yr and currently represent 10–12% of the production of drugs in Colombia.	Herbicides, fungicides, and insecticides are used in the study area but people report very low use of these compounds.	Aerial spraying of glyphosate has been conducted since 1999 and Tumaco accounts for 25–30% of the total spraying in the department of Nariño.
Putumayo	The project was carried out in the municipality of Puerto Asis located at 260 m a.s.l. with an annual mean temperature 27ºC. The area has 68,112 inhabitants, of whom 57.7% live in rural areas. Twenty percent of the total inhabitants are women of fertile age. The population of Putumayo and in the study area is mainly mestizo but people of Indian descent are found in this department.	Small crops of maize, plantain, and cassava are grown for local use.	Herbicides, fungicides, and insecticides are used in the study area. Low use of these compounds is reported by local inhabitants.	In 2003 and 2004, 15–24% of the aerial spraying of coca in Putumayo occurred in this municipality, indicating extensive spraying in the study area.
Sierra Nevada de Santa Marta	The National Park Sierra Nevada de Santa Marta is in the northern part of Colombia and has the highest peaks in the country, reaching more than 5000 m a.s.l. The selected area for the study is at the foothills of the Sierra at 700 m a.s.l. and rainfall of 3000 mm per year. The rural population of Santa Marta has 13,000 women 15–49 yr of age but only one village, where organic crops are cultured, was chosen for the study. The ethnicity of the population of the study area is mestizo but Indian heritage is less prevalent than in Putumayo or Boyacá.	Coffee plantations are the main crop in the study area of this region. Banana, peanuts, oranges, plantain, a type of sweet potato, and cacao, are also grown in the area.	No pesticide use for coffee plantation and other crops. Instead, native plants and biological control of pests are utilized.	None
Valle del Cauca	The study was carried out in the municipalities of Candelaria and Cerrito and the "*corregimiento*" (not large enough to be a municipality) of Rozo. Located at 1000 m .a.s.l. with an annual mean temperature of 24°C. Approximately 13% of the population lives in rural areas. The population in the area includes mestizos as well as people of African origin.	Main crop in Valle del Cauca and in the study area is sugar cane. Coffee, plantain, and banana are also grown to a lesser extent.	Substantial herbicide use in sugar cane including glyphosate.	Aerial spraying of glyphosate for cane maturation 2 wk before harvesting.

smoking, drug, coffee, and alcohol consumption. Data on life style practices and work status for the father were also collected. A variable for self-perception of pollution of water was included, as well as one related to the source of water consumption in the current domicile.

Statistical Analysis

For analysis purposes, if TTP was reported as zero months (or "unexpected"), the answer was interpreted as 1 mo. Cut points for categorization of continuous variables were set as follows: age at time of interview at ≤25 yr; age when attempting to get pregnant and age when first becoming pregnant was set at ≤20 yr. For each exposure and potential confounder variable, analysis of variance (ANOVA) of mean TTP was conducted.

Among the 2592 women, 2477 pregnancies and 12,393 months (11,033 for final model) were included in multivariate models. Each month was classified according to the relevant exposure and confounder variables and an indicator variable was generated for every month, giving information on whether the cycle under this exposure resulted in a pregnancy or not. Fecundability odd ratios (fOR) were calculated with 95% confidence intervals (95% CI) using a discrete time analogue of Cox's proportional hazard model (Baird et al., 1986; Curtis et al., 1999; Zhou & Weinberg, 1999). Because TTP was assessed for a period of 12 mo, a separate censor variable was introduced if a woman took >12 mo to conceive. A value of 0 (noncensored) was used if TTP was ≤12 mo and 1 if TTP was >12 mo. fOR below unity indicate subfertility. All analyses were performed using Stata 7.0 (Stata Corporation, College Station, TX) with macros developed by Dinno (2002).

The initial saturated multivariate model included all variables significant on bivariate analysis ($p < .10$) and variables of prime biological importance (age at time of trying to become pregnant). Several goodness-of-fit statistics for logistic regression were checked: Pearson chi-square, deviance, and Hosmer–Lemeshow statistics (Hosmer & Lemeshow, 1989). The final model consisted of only those variables that contributed to the explanatory value of the model at a .05 level of significance (coefficient of determination). Collinearity was tested with VIF (variance inflation factor). The assumption that the fecundability odds ratio was constant across time (Weinberg & Wilcox, 1998) was tested graphically and by including an interaction term between months to pregnancy and exposure or confounder variables in the final model. The latter were not significant, implying that the proportional assumption was not violated. Finally, to evaluate a possible selection bias based on wantedness, the analyses were repeated excluding the pregnancies occurring in the first month (Weinberg et al., 1994). No significant changes in the final model were observed.

An alternative model without perfect fitting is presented for the sake of research interest, even though it had some marginal variables (p values >.05).

RESULTS

TTP showed large differences in different regions (Table 2). The Department of Valle del Cauca displayed a low percentage for the first month and Boyacá and Nariño were exceptionally high for the twelfth month (Figure 2).

Participating women were generally young (mean and median age 21 yr, range 15–48 yr, but there was one of 54 yr of age) and had completed at least some secondary education (Table 3). The vast majority had regular menstrual cycles (96.7%); a substantial proportion had irregular partner relationships. Most became pregnant first at young ages (73.6% at 20 yr of age or less). During the year before first pregnancy (YBF), most were free of illness (84.3%), had not had x-rays (95.4%), and did not smoke tobacco (95.1%). Alcohol and coffee consumption were 51.8% and 80.3%, respectively.

In the crude analyses (Table 3), longer TTP was associated with region, older maternal age, ethnic group, irregular menstrual cycles, and irregular partner relationship. Previous visits to physician for problems related with fertility, x-rays taken in the year before pregnancy (YBP), and coffee consumption in the YBP were associated with longer TTP. A significant trend between coffee consumption and longer TTP was observed. Maternal overweight showed a borderline significant association with a longer TTP.

The majority of women were housekeepers at the time they become pregnant. A tendency to longer TTP was observed among those engaged in some waged work and with higher education. Paternal unemployment or self work, were associated with longer TTP. No other paternal data were related to the outcome.

Self-perception about bad quality of water was associated with longer TTP, and all sources of water presented risk when they were compared with pure water ("*nacimiento*"), except some few cases that used carried water ("*carro-tanque*").

TABLE 2
Time to Pregnancy and Percentage of Pregnancy by Month in the Study Regions

	Regions					
Months	Boyacá	Nariño	Sierra Nevada de Santa Marta	Putumayo	Valle del Cauca	Total
1	69.2	21.2	25.5	49.4	17.0	36.8
3	82.5	62.9	52.9	56.1	28.7	57
6	88	94.8	72.1	74.9	45.2	75.2
12	96.9	99.3	87.3	89	73.5	89.4
MTTP[a]	3	3.3	8.6	6.4	14	7
MTTP[b]	3	3.3	7.1	6	12.6	6.3

[a]MTTP, mean time to pregnancy in months.
[b]Censored to 60 mo (see text).

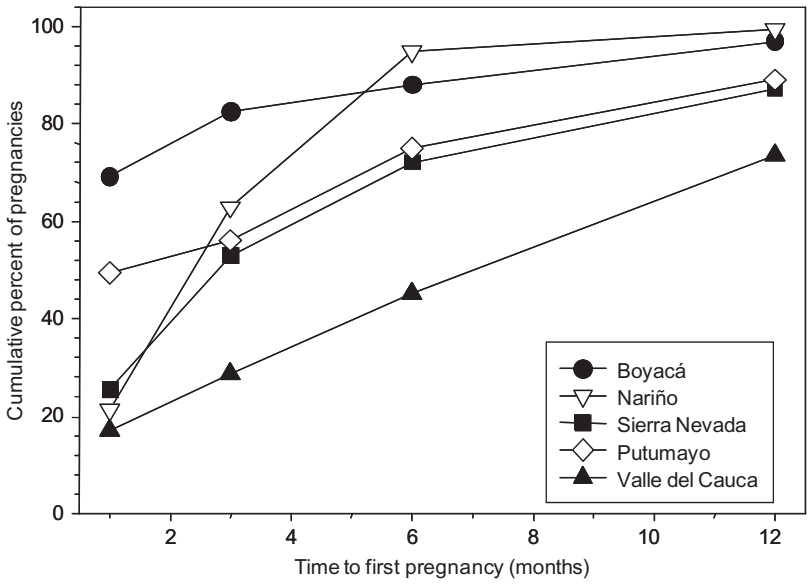

FIG. 2. Unadjusted cumulative percentage of pregnancies over time for the five study regions in Colombia.

In the final multivariate model (Table 4), the main predictor was region adjusted by irregular relationship with partner and maternal age at first pregnancy. Boyacá displayed minimal risk and was used as the reference. Nariño, Sierra Nevada de Santa Marta, and Putumayo showed higher risk, with the highest risk in Valle del Cauca. Goodness-of-fit statistics for the final model were optimal when adjustment for maternal age when the first pregnancy had occurred was carried out. Table 4 shows the analysis without including 159 women who reported visiting a physician because of fertility problems. In the crude analysis, irregular cycles and medication for this purpose were associated with longer TTP, but when potentially subfertile couples were excluded, these two variables were no longer included in the final model. Age at first pregnancy and irregular relationship remained in the model after excluding those with fertility problems. Table 5 shows that coffee consumption and perception of contamination of water, although no longer significant, were borderline. When categorized in number of cups, coffee consumption still showed a positive trend; the greater the number of cups, the longer was the TTP.

An alternative model is presented in Table 5 because that model includes variables such as coffee consumption and water pollution with marginal statistical significance but with strong biological and environmental significance.

DISCUSSION

This was the first study performed in Colombia with the objective of assessing whether an association existed between use of aerially applied glyphosate for eradication of illicit crops and subchronic effects on reproduction, such as TTP**.** A major problem in many epidemiological studies is the lack of appropriate exposure data based on actual measurements (Arbuckle et al., 2002; Harris et al., 2002; Coble et al., 2005; Ritter et al., 2006; Firth et al., 2007). In most cases, exposures are approximated through questionnaires, geographical regions, type of crop, season of application, chemical group, or classification according to mode of action (herbicides, insecticides, fungicides, etc). This is done because most pesticides lack a persistent biomarker, which prevents a measurement-based characterization of exposure for the majority of the pesticide products, including glyphosate (Acquavella et al., 2004).

For this reason, the acute effects of this herbicide are the most extensively documented (Acquavella et al., 1999) with predominant manifestations being eye irritation and other temporary dermal effects. Whether pneumonitis occurs is controversial (Pushnoy et al., 1998), and fatal cases have been recorded only with accidents or when glyphosate was ingested with the purpose of committing suicide (Williams et al., 2000). Some cases of Parkinson's disease have been associated with acute intoxication with glyphosate (Barbosa et al., 2001), but the small number of cases and lack of laboratory animal analogies do not allow assignment of causality.

Some authors have made efforts to identify the compounds used by study subjects. Several studies on different populations that specifically addressed the use of glyphosate were found and published since the last major reviews (Williams et al., 2000; Solomon et al., 2007). Studies related to cancer and to adverse reproductive and developmental effects reported equivocal and unclear relationships between glyphosate use and some reproductive outcomes (Curtis et al., 1999; Arbuckle et al., 2001; Garry et al., 2002; De Roos et al., 2005).

TABLE 3
Mean Time to Pregnancy (Without Censoring) and Crude Fecundability Odds Ratio (fORc) Analyzed by Different Sociodemographic Characteristics

Variable	*n*	Time to pregnancy (mo), *X* (SD)[a]	fORc ($CI_{95\%}$)[b]	*p*
Region				
Boyacá	582	3 (4.7)	1	–
Nariño	552	3.3 (3.3)	0.72 (0.62, 0.83)	<.01
Sierra Nevada de Santa Marta	551	7.1 (10.3)	0.41 (0.35, 0.48)	<.01
Putumayo	535	6 (8.3)	0.44 (0.38, 0.51)	<.01
Valle del Cauca	531	12.6 (13.5)	0.2 (0.17, 0.24)	<.01
Maternal age (yr)				
≤25	2356	5.7 (8.2)	1	–
>25	395	10 (14)	0.64 (0.56, 0.73)	<.01
Age to first pregnancy (yr)				
≤20	2026	5.5 (8)	1	–
>20	725	8.6 (12.3)	0.69 (0.62, 0.76)	<.01
Age at start TTP study period (yr)				
≤20	2094	6.2 (9)	1	–
>20	657	6.8 (10.5)	0.98 (0.88, 1.1)	.69
Ethnic group				
Mestizo	2121	6.5 (9.6)	1	–
Negro	508	6.3 (9.6)	1. (0.9, 1.14)	.83
Indígena	49	3.7 (4.1)	1.37 (0.9, 1.94)	.08
Zambo	41	3.6 (2.6)	1.38 (0.95, 2.01)	.09
Mulato	32	3.3 (2.6)	1.6 (1.05, 2.51)	.03
Grouped ethnic group				
Mestizo and Negro	2629	6.45 (9.6)	0.7 (0.56, 0.87)	<.01
Indígena, Zambo, and Mulato	122	3.54 (3.2)	1	–
Education				
None	42	4.9 (9.1)	1	–
Incomplete elementary school	582	4.6 (7.1)	0.93 (0.63, 1.39)	.74
Complete elementary school	526	5.6 (7.7)	0.76 (0.51, 1.13)	.17
Incomplete high school	459	7 (10.3)	0.66 (0.45, 0.98)	.04
Complete high school	130	9.7 (12.5)	0.47 (0.31, 0.73)	<.01
Zone				
Urban	5	15.2 (18.6)	–	–
Rural	2743	6.3 (9.4)	–	–
Marital status[c]				
Common law	1010	5.1 (8.3)	1	–
Not common law	1741	7 (9.9)	0.71 (0.64, 0.78)	<.01
Socioeconomic status[c,d]				
0	38	4.8 (5.8)	1.1 (0.75, 1.63)	.62
1	2013	6.4 (9.4)	1	–
≥2	493	6.6 (10.1)	1.03 (0.91, 1.17)	.60
Nutritional status[e]				
Low weight	111	7.1 (10.9)	0.91 (0.72, 1.15)	.42
Normal weight	2453	6.2 (9.3)	1	–
Overweight	184	7.2 (10.0)	0.83 (0.69, 1.00)	.04
Maternal work[c]				
Administrative, teacher, or student	678	6 (8.6)	0.99 (0.89, 1.11)	.92

(*Continued*)

TABLE 3
(*Continued*)

Variable	*n*	Time to pregnancy(mo), *X* (SD)[a]	fORc (CI $_{95\%}$)[b]	*p*
Home, no work, housekeeper	1631	6 (9.2)	1	–
Community mother, mining, various, other, occasional	229	8.7 (11.9)	0.7 (0.59, 0.83)	<.01
Health worker, independent worker, seller	126	8.7 (12.3)	0.74 (0.59, 0.93)	.01
Agriculture and floriculture	86	4.2 (4.6)	1.14 (0.87, 1.48)	.34
Maternal work in cocaine[c]				
No	2743	6.3 (9.4)	1	–
Yes	8	7.6 (7.4)	0.67 (0.29, 1.54)	.35
Menarche age (yr)				
<12	1031	6.6 (10)	1	–
13	802	5.8 (8.6)	1.06 (0.94, 1.19)	.32
14	523	6.4 (9.3)	1.02 (0.89, 1.16)	.81
15	392	6.6 (9.4)	0.94 (0.82, 1.09)	.43
Menstrual cycle				
Regular	2612	6.2 (9.3)	1	–
Irregular	88	9.5 (12.3)	0.64 (0.49, 0.84)	<.01
Previous consultation for pregnancy problems				
No	2592	5.8 (8.7)	1	–
Yes	159	15.2 (14.4)	0.33 (0.27, 0.41)	<.01
Smoking[c]				
No	2616	6.3 (9.5)	1	–
Yes	135	6.2 (7.9)	0.95 (0.77, 1.17)	.63
Alcohol consumption[c]				
No	1325	6.2 (9.4)	1	–
Yes	1425	6.3 (9.4)	0.97 (0.88, 1.06)	.52
Coffee consumption[c]				
No	543	5.3 (8.1)	1	–
Yes	2208	6.6 (9.7)	0.81 (0.72, 0.91)	<.01
Number of coffee cups/day[c] **				
0	543	5.3 (8.1)	1	–
1 to 3	1916	6.4 (9.5)	0.83 (0.73, 0.93)	<.01
≥4	292	7.4 (10.7)	0.73 (0.61, 0.87)	<.01
X-rays[c]				
No	2616	6.2 (9.2)	1	–
Yes	125	9.4 (12.5)	0.67 (0.54, 0.84)	<.01
Any kind of illness[c]				
No	2316	6.3 (9.3)	1	
Yes	432	6.4 (9.7)	0.97 (0.86, 1.10)	.68
STD[c,e]				
No	2717	6.3 (9.3)	1	–
Yes	27	7.3 (10.4)	0.84 (0.52, 1.38)	.50
Medication for regularizing menses[c]				
No	2721	6.3 (9.4)	1	–
Yes	30	11.2 (10)	0.45 (0.28, 0.71)	<.01
Medication for “sugar in blood”[c]				
No	2735	6.3 (9.4)	1	–

(*Continued*)

TABLE 3
(*Continued*)

Variable	*n*	Time to pregnancy(mo), *X* (SD)[a]	fORc (CI $_{95\%}$)[b]	*p*
Yes	16	7.6 (6.5)	0.7 (0.39, 1.24)	.22
Other medications[c]				
No	2027	6.8 (9.7)	1	–
Yes	703	5 (8.3)	1.36 (1.22, 1.51)	<.01
Paternal work[c]				
Administrative or student	160	6.3 (8.2)	0.86 (0.7, 1.05)	.14
No work, occasional	212	8.4 (12.5)	0.74 (0.61, 0.88)	<.01
Carpenter, driver, construction, mining, mechanic, industrial timbering	507	5.7 (9)	1.02 (0.89, 1.16)	.80
Other, health worker, independent worker, vendor	713	7.7 (10.8)	0.75 (0.67, 0.84)	<.01
Agriculture, floriculture, livestock	1157	5.4 (7.9)	1	–
Paternal work in cocaine[c]				
No	2457	6.4 (9.6)	1	–
Yes	292	5.5 (7.8)	1.07 (0.92, 1.24)	.40
Any disease of the father[c]				
No	2398	6.4 (9.5)	1	–
Yes	248	6.8 (9.4)	0.93 (0.80, 1.1)	.41
STD of the father[c,f]				
No	2608	6.4 (9.5)	1	–
Yes	37	6.1 (8.2)	0.99 (0.66, 1.47)	.94
Paternal alcohol consumption[c]				
No	1325	6.2 (9.4)	1	–
Yes	1425	6.4 (9.4)	0.97 (0.88, 1.06)	.52
Paternal smoking[c]				
No	2143	6.2 (9.3)	1	–
Yes	538	6.9 (10)	0.9 (0.80, 1.01)	.08
Paternal use of psychotropic drugs[c]				
Yes	2619	6.4 (9.5)	1	–
No	54	4.5 (5.7)	1.23 (0.88, 1.72)	.22
Perceived contamination of water				
No	1218	6 (9.2)	1	–
Yes	1533	6.6 (9.5)	0.9 (0.82, 0.98)	.02
Source of drinking water				
Municipal tap water	598	7.2 (11)	1.13 (1, 1.28)	.05
Rain water	65	5.3 (8)	1.38 (1.02, 1.88)	.04
Stream, ravine, or creek	257	6.1 (10.2)	1.36 (1.14, 1.61)	<.01
"Carried water"	10	14.8 (16.5)	0.44 (0.19, 1.05)	.07
"Pure water"	311	3.7 (5.7)	2.03 (1.73, 2.39)	<.01
Deep well	1040	7.4 (10)	1	–
River	470	4.6 (6.5)	1.52 (1.33, 1.74)	<.01

**There is a significant trend when $p < .05$.

[a]Mean and standard deviation.

[b]Crude fecundability odds ratio; 95% confidence interval.

[c]During the year prior to pregnancy.

[d]The population is classified in 6 socioeconomic strata, from 1 being the lowest to 6 the highest. A zero indicates extreme poverty.

[e]Based on self-reporting images scaled from 1 to 9. Low weight 1 to 4, normal 5 to 7, overweight 8 and 9 (BMI ≥25) (Madrigal-Fritsch et al., 1999).

[f]STD, sexually transmitted disease.

TABLE 4
Causes of Fecundability Adjusted[a] for the Relationship Between Time to Pregnancy (TTP) and Region[b]

Variable	fRMa[c]	EE[d]	IC $_{95\%}$[e]	*p*
Region[f]				
Nariño	0.53	0.044	0.45, 0.63	<.01
Sierra Nevada	0.36	0.030	0.30, 0.42	<.01
Putumayo	0.34	0.029	0.29, 0.41	<.01
Valle del Cauca	0.15	0.013	0.12, 0.18	<.01
Age at first pregnancy >20 yr[g]	0.81	0.048	0.72, 0.91	<.01
Irregular relationship with father[h]	0.76	0.041	0.68, 0.84	<.01

Note. n = 2592 mothers 11,270 cycles.
[a]Proportional risk model of Cox, modified after Dinno, (2002).
[b]Restricted to those mothers who did not consult a physician regarding problems in conceiving.
[c]fRMa Adjusted cause of fecundability.
[d]Standard error.
[e]95% Confidence interval.
[f]Compared to Boyacá as reference.
[g]Compared to ≤20 years as reference.
[h]Compared to regular relationship as reference.

TABLE 5
Causes of Fecundability Adjusted[a] for the Relationship Between Time to Pregnancy (TTP) and Region[b] Based on an Alternative Model

Variable	fRMa[c]	EE[d]	IC$_{95\%}$[e]	*p*
Region[f]				
Nariño	0.56	0.048	0.47, 0.66	<.01
Sierra Nevada	0.36	0.031	0.31, 0.43	<.01
Putumayo	0.35	0.029	0.29, 0.41	<.01
Valle del Cauca	0.15	0.014	0.13, 0.18	<.01
Age at first pregnancy >20 yr[g]	0.81	0.048	0.73, 0.91	<.01
Irregular relationship[h]	0.76	0.041	0.68, 0.84	<.01
Consumption of coffee[i]				
Medium (1–3 cups per day)	0.91	0.059	0.81, 1.04	.15
High (4 and more cups per day)	0.84	0.083	0.69, 1.02	.08
Perception of contamination of water[j]	0.91	0.51	0.81, 1.01	.08

Note. n = 2592 mothers, 11,270 cycles.
[a]Proportional risk model of Cox, modified after Dinno (2002).
[b]Restricted to those mothers who did not consult a physician regarding problems in conceiving.
[c]fRMa Adjusted cause of fecundability.
[d]Standard error.
[e]95% Confidence interval.
[f]Compared to Boyacá as reference.
[g]Compared to ≤20 years as reference.
[h]Compared to regular relationship as reference.
[i]Compared to no consumption as reference.
[j]Compared to no contamination as reference and based on self-perception and source of water normally consumed.

Other risk factors present in the rural and agricultural environment of the women studied and individual characteristics (genetic, for example) may be associated with TTP. Longer TTP were observed in some populations with higher physical activity (Florack et al., 1994) or psychological distress (Hjollund et al., 1999). Further, TTP may be influenced by knowledge and behavior, such as patterns of intercourse as well as biologic factors (Joffe et al., 2005), and these need to be considered as potential confounders (Tingen et al., 2004; Stanford & Dunson, 2007) The potential effect of these factors on TTP could not be isolated in this study, even though the fOR was adjusted for most known confounders and independent predictors.

As shown in Figure 2, there was no difference in cumulative TTP between Putumayo, where illicit crops were sprayed, and Sierra Nevada, where there was no herbicide use. In turn, the latter region showed lower cumulative percent pregnancies than Nariño, an eradication spray area, and Boyacá, where there is agricultural herbicide use but manual eradication of illicit crops. Although classification of exposure may be a source of bias in this type of study, no relationship between reduced fecundability in the studied regions and use of glyphosate specifically for spray eradication or use of pesticides in general can be established from our data. Prospective studies that prevent or reduce classification bias of exposures are recommended to further elucidate relationships between aerial spraying of glyphosate for eradication, agricultural pesticide use, and human health indicators.

Pesticides in general are likely not the cause either, as large differences in TTP were observed between two regions of high to moderate pesticide use, Valle del Cauca and Boyacá. The observed ecological differences remain unexplained, but may be produced by varying exposures to environmental factors, history of contraceptive programs in the region, or psychological distress. Future studies examining these causes are needed.

Table 3 shows crude association between coffee consumption and longer TTP with a significant trend. This association is not significant in the adjusted model but the level of significance was borderline. Published results regarding coffee or caffeine consumption and TTP are not conclusive. Some studies showed no association (Joesoef et al., 1990; Alderete et al., 1995), but other investigators found that coffee drinkers have a lower risk of pregnancy (Wilcox et al., 1988; Christianson et al., 1989; Williams et al., 1989; Hatch & Bracken, 1993; Curtis et al., 1997). This relationship needs to be further investigated.

Distribution of pregnancies in relation with months in different regions showed great differences (Table 2). In a previous study in Colombia (Idrovo et al., 2005), the percentage for first month was close to 30%, which is lower than more than 40% reported from a Danish study (Joffe et al., 2005). In our study, the region of Valle del Cauca showed a low percentage and Boyacá exceptionally high for first and twelfth months (Figure 2). The mean for 12 mo in developed countries is between 85 and 90%. These results are consistent with the National Survey of Demography and Health (Ojeda et al., 2005) that showed Boyacá as the Department with the lowest proportion of women who reported fertility problems (4.2%). Valle del Cauca (11.2%) and Magdalena (16.1%), where Sierra Nevada is located, were above the national average (10.6%).

A retrospective assessment of TTP as an outcome variable was conducted to evaluate ecological exposure to glyphosate. Although it is widely recognized that retrospective studies for TTP can be carried out, they are prone to some biases that need to be taken into account in the interpretation of our results. Difference in sexual behavior between exposed and nonexposed subjects, particularly in frequency of intercourse, has been pointed out as source of bias (Tingen et al., 2004; Stanford & Dunson, 2007). Women of reproductive age differed in reporting intercourse in the last 4 wk, from 48.8% in Boyacá and neighboring departments to 53.8% in the Pacific region where Tumaco (Nariño) is located (Ojeda et al., 2005). Couples who had not used contraception in the last year were included and, in the multivariate analysis, those who had had consultation because of fertility problems were excluded. These two criteria excluded those who may have become pregnant while using contraception (highly fecund couples) and subfertile couples (Bonde et al., 2006). Studies also evaluated whether there were other sources of bias such as pregnancy recognition (Joffe et al., 2005) by asking whether a miscarriage occurred, and thus it was possible to control for this variable. However, biological factors such as age at first pregnancy and use of contraception in the past were taken into account as these appear to be more important than lifestyle factors in assessing TTP (Axmon et al., 2006).

Classification of exposure was by location of residence. Nonexposed participants were those who lived in the region where organic crops were produced and who, in addition, did not report any use of pesticides in the interview. In the other four departments, there was exposure not only to glyphosate, but also to other herbicides and pesticides. Although place of residence is not an accurate surrogate for exposure to pesticides and may generate misclassification (Arbuckle et al., 2004), this ecological assessment is useful to explore, at the population level, whether an association exists between the putative exposure (aerial spraying of glyphosate) and outcome (Ritter et al., 2006). However, in this study, aerial spraying of glyphosate was not consistently associated with delayed time to pregnancy.

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