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RESEARCH ARTICLE

# Residential proximity to pesticide applications in Argentine Patagonia: impact on pregnancy and newborn parameters

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## Abstract

Among residents living close to agricultural fields who are potentially exposed to pesticides, pregnant women and their fetuses are of particular concern for their vulnerability to environmental chemicals. In this collaborative multicenter study, we covered a wide distribution of participants in the most important fruit production zone of north Patagonia (Argentina) to investigate whether maternal residential proximity to fruit croplands with intense pesticide applications (rural group –RG-) is associated with pregnancy complications and alterations in their newborn parameters compared to the urban population (urban group –UG-). A total of 776 pregnant women met the inclusion criteria. The percentage of threatened miscarriage was significantly higher in the RG than in the UG. The percentage of miscarriage, threat of premature labor, intrauterine *fetal death,* preterm premature rupture of membranes, and intrauterine growth retardation were similar in both groups. Newborn anthropometric parameters were corrected by sex and gestational age prior to statistical analysis. Length at birth and head circumference were lower in the RG than in the UG. Birth weight was similar in both groups. The percentage of head circumference less than the 5th percentile and the ponderal index were greater in the RG than in the UG. Our results suggest that proximity to pesticide applications may increase the risk of pregnancy complications and altered newborn parameters.

**Keywords** Prenatal exposure · Pregnancy · Organophosphates · Distance to fruit crops · Neonicotinoids · Newborn ponderal index

Gladis G. Magnarelli and María Gabriela Rovedatti contributed equally to this work.

**Highlights**

- Higher threatened miscarriage was the pregnancy complication associated to residential proximity to Patagonian fruit croplands with pesticide applications.
- Lower length at birth was associated to residential proximity to the fruit croplands in High Valley of Negro River, in Argentine Patagonia.
- Women living within a short distance of this agricultural field had babies with lower head circumference at birth.
- Higher ponderal index in newborns was associated to residential proximity to this fruit-growing zone.

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## Introduction

Many non-farmworker residents living within a short distance of agricultural fields may be exposed to spray drift emissions from pesticides designed to target field pests, both during and after applications (Rowe et al. 2016). Due to the intrinsic toxicity of pesticides, it is important to evaluate the potential health consequences in this specific population. However, to date, this issue has been little studied. Pesticides are transported mainly by wind and rain from their points of application to neighboring crops and land, and from the soil to surface and subsurface waters (Matthews and Hamey 2003; Fenik et al. 2011). Some of these pesticides, including organophosphates (OPs) and carbamates (CBMs), share at least one mode of action, the inhibition of cholinesterases, and there is *in vitro* evidence that the exposure to certain pesticide mixtures may have additive inhibitory effects (Mwila et al. 2013). Pesticide residues in house dust (Coronado et al. 2006; Lu et al. 2000) and pesticide metabolites in children (Babina et al. 2012; Bradman et al. 2011; Fenske et al. 2005; Muñoz Quezada et al. 2019) have been found in populations residing close to agricultural areas. Although pesticide biomarkers such as dialkyl phosphate metabolites are important tools to assess exposures to pesticides, several challenges limit their utility in epidemiological analyses. For example, many pesticides have a short half-life in the body, and biomarkers reflect only very recent exposures (in the order of hours to days) (Bradman et al. 2013).

Among residents living close to agricultural fields potentially exposed to pesticides, pregnant women and their fetuses are of particular concern for their vulnerability to environmental chemicals (Stillerman et al. 2008). One reason for this is that, during fetal development, which is a process characterized by marked cellular proliferation and development of numerous changing metabolic capabilities in the organism, there are critical windows of susceptibility during which exposures to environmental contaminants may result in adverse, permanent, and irreversible effects that can have lifelong and even intergenerational impacts on health (Woodruff et al. 2008). Therefore, during critical periods of development, exposure to pesticides can result in increased risk for pregnancy complications (Magnarelli et al. 2011) and adverse health outcomes (Béranger et al. 2020; Koureas et al. 2012; Weselak et al. 2007). In fact, decreased fetal growth (Eskenazi et al. 2004; Whyatt et al. 2004; Petit et al. 2010), decreased birth weight (BW) and length at birth (LB) (Perera et al. 2003; Rauch et al. 2012; Wohlfahrt-Veje et al. 2011), shortened gestation (Eskenazi et al. 2004; Harley et al. 2011; Jaacks et al. 2019; Parvez et al. 2018; Rauch et al. 2012; Whyatt et al. 2004), and increased risk of *in utero* growth restriction (Levario-Carrillo et al. 2004) and birth defects (Carmichael et al. 2014; Winchester et al. 2009) have been associated with exposure to pesticides. In addition, delayed conception, miscarriage, and stillbirths have been related to exposure to OPs (Arbuckle et al. 2001; Hanke and Jurewicz 2004; Pastore et al. 1997). Other studies have also shown that prenatal exposure to OPs may impact the neurodevelopment of newborns (Woskie et al. 2017) and pre-school children (Wang et al. 2017) and has also been associated with cognitive abilities in school-age children (Bouchard et al. 2011; Friedman et al. 2020; Rauh et al. 2011). Moreover, epidemiological studies have shown that higher nearby agricultural pesticide use (Shelton et al. 2014) and prenatal exposure to OPs (Sagiv et al. 2018) are associated with autism.

The Alto Valle del Río Negro (High Valley of Negro River), in Argentine Patagonia, is a fruit-growing zone where two periods of the year are clearly differentiated: one in which pesticides, mainly OPs, are intensively applied, known as the spraying period, and another period in which no pesticides are applied, known as the non-spraying period. To evaluate the effects of pesticides, at our lab, we have studied mothers and children residing in this area for more than fifteen years by sampling blood of pregnant women (Souza et al. 2005; Cecchi et al. 2012; Santa- Cruz et al. 2020; Vera et al. 2012). It is remarkable that, in every sampling of pregnant women's blood, we reported plasma cholinesterase inhibition (18–23%) in the spraying period, which indicates that the population is exposed to OPs. We also studied umbilical cord blood (Quintana et al. 2017), term placentas (Bulgaroni et al. 2013; Chiapella et al. 2014; Rivero - Osimani et al. 2016; Sánchez et al. 2015; Vera et al. 2012), and saliva (Bulgaroni et al. 2012). In addition, we have recorded pregnancy complications (Santa-Cruz et al. 2020) and anthropometric parameters of newborns (Cecchi et al. 2012; Quintana et al. 2017; Rivero - Osimani et al. 2016; Santa- Cruz et al. 2020; Souza et al. 2005) in two rural localities of the area. Data for these studies were obtained both from the rural population during the spraying and non-spraying periods and from the urban population. We also conducted personal interview surveys and found that people had risk behaviors and little knowledge about pesticide applications in the area (Rovedatti et al. 2006). Additionaly, we found alterations in the antioxidant defense and immune response, as well as DNA damage and endocrine disruption (Bulgaroni et al. 2013; Cecchi et al. 2012; Quintana et al. 2017).

In this work, we conducted a collaborative multicenter study with the objective to expand the sampling covering of the Alto Valle del Río Negro in order to investigate whether maternal residential proximity to fruit croplands with intense pesticide applications is associated with pregnancy complications and alterations in their newborn parameters. This is the first study in Argentine Patagonia that compares pregnancy complications and newborn parameters between the rural and urban population by including data from most of the localities of this important fruit production zone.

## Materials and methods

### Characteristics of the study area

The Alto Valle del Río Negro (Fig. 1) is an artificially irrigated valley which is the Argentine region with the largest agricultural fruit production. Approximately 50,000 ha produce 1,800,000 tons of pears and apples, with 1,368,000 tons being exported (Ministry of Public Finance, Presidency of Argentina 2016). This area includes two Argentine provinces: Río Negro and Neuquén, in northern Patagonia (39° 01′1S and 67° 40′W), and comprises Neuquén city, with a population of ≅231,000 inhabitants, other localities which have between 5000 and 80,000 inhabitants, and other rural areas and small towns surrounded by farms. The soils have scarce organic matter (< 1%). The climate is continental, temperate, and arid, with annual rainfall totals of about 200 mm and frequent spring freezes. The strongest winds, which come from the west and south-west, occur in spring.

Croplands with higher productivity are small agricultural properties of 5.1–50 ha in size, where 500 tons of pesticides are applied every year for fruit pest control (FunBaPa 2010). The insecticide families mostly used in this region are OPs (such as chlorpyrifos and azinphos-methyl) and CBMs (such as carbofuran and pirimicarb). In addition, neonicotinoids (NNTs), such as tiacloprid and acetamiprid, are currently being introduced in the market. Pesticides are applied at the average fruit tree height by ground-based spraying equipment every 15 days for three/four consecutive months (October-December/January) during the dry seasons. In addition, artificial irrigation is performed by periodic flooding of the fruit orchards, which have a flat topography that would enable the transport of pesticides from the soil to surface and subsurface waters. Although an integrated pest management based on selective insecticides, biopesticides, and sexual confusion technique is also implemented in the area, several studies have reported the presence of pesticide residues in the soil (Kirs 2002), water compartments (Loewy et al. 2011; Tosi et al. 2009), and drainage channels (Macchi et al. 2018).

### Population and study design

In this prospective study, healthy pregnant women between 17 and 35 years old were recruited in public hospitals of the localities of Allen, Cinco Saltos, Cipolletti, and General Roca, located in the province of Río Negro, and in public hospitals of San Patricio del Chañar and Neuquén cities, and San Lucas Clinic, located in the province of Neuquén. Pregnant women were consecutively recruited by biochemists during routine laboratory prenatal care visits from July 2009 to May 2011. They were informed about the objectives and modalities of the study and asked to sign a written informed consent in accordance with procedures approved by the Bioethics Committee of the local Advisory Committee of Biomedical Research in Humans. The study desing did not require pregnant women to attend beyond the normal prenatal care protocol. They were followed during pregnancy until delivery. At the moment of recruitment, a prenatal questionnaire designed for this study was orally administered to obtain information on the permanent residential address, sociodemographic characteristics, and lifestyle habits such as smoking, consumption of groundwater, alcohol and

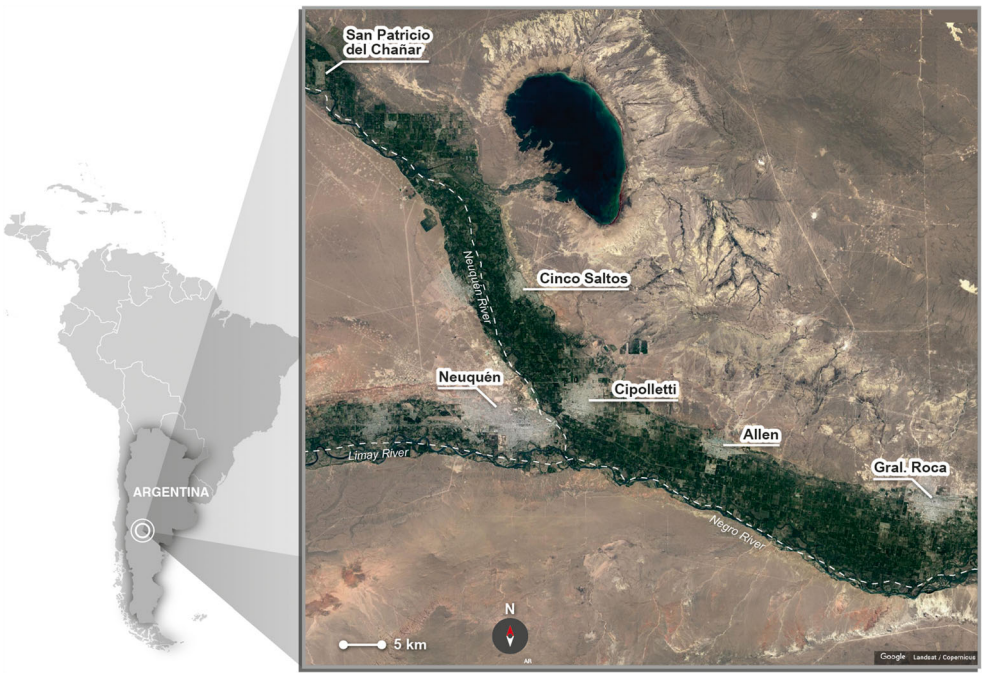


**Fig. 1** Geographic location of the study area, Alto Valle del Río Negro, and sampling localities

medicines, previous history of pesticide exposure, and domestic pesticide spraying. This last item referred to pesticide use at home, garden, or workplace and concerned the application of pesticides with a fumigation device and not the use of household aerosols.

Distance between the women's home and the nearest cropland was estimated locating their addresses in Google Maps. Based on the above, participants were divided into two groups: the rural population group (RG) and the urban population group (UG). The RG included women living in the proximity to areas of intensive pesticide application (< 5000 m). This distance reflects a potential spray drift range likely to occur during pesticide applications (Bukasala et al. 2018; Copes 2012; van den Berg et al. 1999). The UG consisted of women residing in Neuquén city without previous history of pesticide exposure.

Women were eligible to participate in the study if they were healthy, self-reported ethnicity was Hispanic, were not involved in agricultural work, had been living in the same residential address for more than 4 years, and planned to continue receiving prenatal care at the participating health centers. Women with a multiple pregnancy, thyroidopathy, arterial hypertension, gestational diabetes, and/or cholestasis of pregnancy, as well as those exposed to X rays, on medication (except those included in Group A according to the U.S. FDA), consuming alcohol or drugs, positive for Chagas disease, HIV and/or Toxoplasmosis, and/or serious pregnancy complications such as eclampsia or preeclampsia were excluded from the study. The unit of analysis was the pregnant woman and her newborn delivered by vaginal or cesarean delivery. For sample size calculation, the percentage of women with pathological pregnancies in Neuquén province during 2006 and 2007 was obtained from the Perinatal Information System, Department of Statistics, Secretary of Health, Neuquén province, Argentina. Gynecologists and obstetricians participated by providing information about gestational length based on the last menstrual period and obstetrical adjustment by first ultrasound at 24 weeks of gestation, and about complications during pregnancy. They also provided information about weight gain during pregnancy, complications of labor and delivery, method of delivery, placental characteristics, and newborn anthropometric parameters. Incomplete data were completed revising participants' medical charts, following the delivery of their babies.

## Indicators of pregnancy alterations

Pregnancy alterations considered were threatened miscarriage, miscarriage, threat of premature labor, fetal death, preterm premature rupture of membranes (membrane rupture < 37 weeks of gestation), and intrauterine growth retardation (estimated fetal weight by ultrasound examination of < 10th percentile or birth weight of < 10th percentile for gestational age).

## Fetal growth indicators

Information on birth outcomes, including BW, LB, head circumference (HC) (which is a cranial growth indicator) and neonatal sex, was retrieved. The ponderal index at birth (PI), known to be a good indicator of fetal nutrition and a measure of proportionality to reflect adiposity in infants, was calculated as the ratio of BW in grams to BL in cubic centimeters ($g/cm^3$). Immediately after birth, the newborn's weight (in grams) to the nearest 10 g on a calibrated pediatric scale, and length (in centimeters) were recorded. HC (in centimeters) was recorded 24–48 h after delivery. Measurements were performed using standardized procedures by trained study staff. Preterm birth was defined as delivery at < 37 weeks' gestation. Low birth weight was defined as birth weight < 2500 g. Small for gestational age was defined as weight-for-gestational age percentile < 10 based on the INTERGROWTH-21st standards (Cheikh Ismail et al. 2013).

## Statistical analysis

BW, LB, and HC were corrected by sex and gestational age by using z scores. The *Z*-score was estimated with a transformation of data that indicates how far and in what direction (positive vs. negative) a measured value deviates from the population 50 percentil ($p_{50}$), expressed in units of the population standard deviation (SD). It is a dimensionless quantity derived from dividing the difference between individual value ($x$) and $p_{50}$ by the population SD ($\sigma$): $z = \frac{x - p_{50}}{\sigma}$ (Lejarraga and Fustiñana 1986; Wang and Chen 2012). Percentages were calculated for categorical variables, and mean and SD for quantitative variables. The normality of continuous variables was verified by the modified Shapiro-Wilks test (Mahibbur and Govindarajulu 1997). Statistical analyses of categorical variables were compared using Pearson's chi-squared test. The Student t-test was used to compare differences in the study populations between the two study groups in variables with normal distribution. The Infostat® software was used and statistical significance was assumed as $p < 0.05$.

## Ethics

The study was conducted in accordance with the Declaration of Helsinki of the 59th WMA General Assembly guidelines for the protection of human subjects. The study protocol was approved by the ethical committee of the local Advisory Committee of Biomedical Research in Humans.

## Results

A total of 804 women met the inclusion criteria and responded the questionnaire; 21 of them were excluded from the protocol after developing preeclampsia and 7 were lost to follow-up for different reasons (mainly failure to attend programmed visits or moving before delivery). Therefore, results were based on 776 pregnant women (RG, n = 418; UG, n = 358).

Table 1 shows the description of the sociodemographic characteristics of the women enroled in the study. The average age of mothers at the time of recruitment was 25.6 years (range 17–35) in the UG and 24.6 (range 17–35) in the RG. About 60 % of the women had complete high school education background. In the UG, about 10% of women had an education background greater than high school and in the RG, about 6%. The percentage of women with only complete elementary education was twice as high in the RG as in the UG. In both groups, parity was similar, and about 12–13% of women were malnourished according to Rosso-Mardones chart used during the pre-natal control (Mardones and Rosso 1997). Alcohol intake during pregnancy was occasional, and active and passive smoking during pregnancy, groundwater consumption, and domestic pesticide spraying were greater in the RG. Within the RG, 36% of the mothers were passive smokers during pregnancy compared to 5% in the UG; 6% of women in the RG consumed alcohol once or twice a week compared to 0.6% of women in the UG.

Because recognized confounders such as malnutrition (Wigle 2008), smoking (Salihu and Wilson 2007), and alcohol consumption (Ortega-García et al. 2012) differed between the UG and the RG, we analyzed pregnancy complications and newborn's parameters, first including and then excluding pairs of mother-babies with those characteristics (Fig. 2 and 3).

Figure 2 shows the pregnancy complications recorded. The percentage of threatened miscarriage was significantly higher in the RG than in the UG (03 vs. 3, $p < 0.05$). This result was still significantly higher in the RG when smokers, alcohol consumers, and malnourished women were not considered in the analysis (0 vs. 2.2, $p < 0.05$). The percentage of intrauterine growth retardation, preterm premature rupture of membranes, intrauterine fetal death, fetal death, threat of premature labor, and miscarriage were similar in both groups.

The placental characteristics were analyzed only in a subgroup of patients (UG, n = 42; RG, n = 83). The UG presented no abnormalities, whereas in the RG, 27% presented placental calcifications. When smokers, alcohol consumers, and malnourished women were not considered in the analysis, placental calcification represented 17% of the cases in the RG.

The gestational age for the UG newborns ranged from 28 to 41.5 weeks (mean 38.7 weeks, SD = 1.9 weeks) whereas that for the RG newborns ranged from 31 to 42 weeks (mean 38.0 weeks, SD = 1.5 weeks). Figure 3 shows anthropometric parameters and indexes. The PI was higher in the RG than in the UG, both when considering and not considering all participants with the criterion explained above. The ratio between HC and BW were similar in both groups. Newborn BW, LB, and HC were corrected by sex and gestational age prior to statistical analysis using Z-scores. BW did not differ between groups but LB and HC were lower in the RG than in the UG (Table 2).

Figure 4 shows that the percentage of newborns delivered by cesarean section was higher in the RG than in the UG, considering and not considering all participants. The

**Table 1** Description of sociodemographic characteristics of pregnant women

| | | UG (n = 358) | RG (n = 418) |
|---|---|---|---|
| Age (years) | | 25.6 ± 6.6 | 24.6 ± 6.3 |
| Level of education (%) ** | Elementary complete | 23.5 | 41.2 |
| | High school complete | 66.3 | 53.0 |
| | Greater | 10.2 | 5.8 |
| Parity (n° (%)) | | | |
| 0 | | 41.8 | 40.2 |
| 1 | | 24.1 | 23.2 |
| 2 or more | | 32.7 | 33.0 |
| Nutritional status (%) | Malnutrition | 13.2 | 12.0 |
| Maternal tobacco status (%)** | Active | 1.4 | 8.9 |
| | Passive | 4.9 | 35.5 |
| Alcohol consumption^ (%)** | | 0.6 | 6 |
| Groundwater consumption (%)** | | 0.6 | 8.5 |
| Domestic pesticide spraying (%) ** | | 1.4 | 26.4 |

Results are expressed as means ± SD or as percentage when indicated; *UG*, urban group; *RG*, rural group; ^, occasional (once or twice a week); missing values < 5%. Continuous variables were analyzed by *T*- test and discrete variable by $\chi^2$ , ** $p < 0.01$

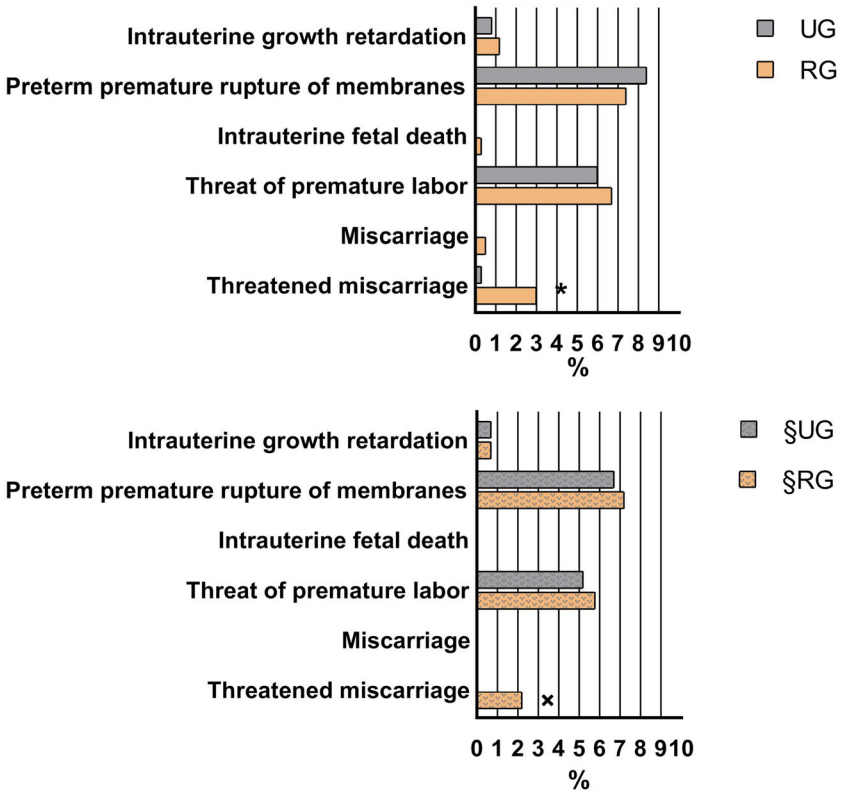


**Fig. 2** Pregnancy complications. UG: urban group, RG: rural group; §: data after excluding pregnant women with malnutrition, active and passive smokers, and alcohol consumers; 5% of missing values. $\chi^2$, *p < 0.05 UG (n = 358) and RG (n = 418), $^{x}p < 0.05$ §UG (n = 269) and §RG (n = 139)

percentage of post-term and preterm birth, the percentage of babies who were small and large for gestational age were similar in both groups. In the RG, without considering smokers, alcohol consumers, and malnourished women, the percentage of HC less than the 5th percentile was greater than that of the UG.

## Discussion

Residential proximity to agricultural pesticide applications may be an important source of environmental exposure. The magnitude of exposure of populations living in the proximity to agricultural fields can be substantially larger than that of populations who are not (Ryberg et al. 2018). People living in agricultural communities are exposed to a complex mixture of many individual pesticide active ingredients as well as to potentially toxic adjuvants included in the formulation. In the present study, we investigated the potential association of maternal residential proximity to fruit croplands with intense pesticide applications during pregnancy on pregnancy complications and alterations in their newborn parameters in Argentine North Patagonia. As the variability in fetal growth parameters at birth is known to be associated with the sex of the baby, gestational age at birth, multiplicity, and ethnicity (Janssen et al. 2007), women with similar parity and ethnicity were included in the study, and results were corrected by sex and gestational age. We observed increased pregnancy complications and altered fetal growth parameters in the population with maternal permanent residence closer than 5000 m from fruit croplands (RG), where OPs are the principal pesticides applied.

Among pregnancy complications, the percentage of threatened miscarriage, which, as defined by the World Health Organization, is a pregnancy-related bloody vaginal discharge or frank bleeding during the first half of pregnancy without cervical dilation, was three times greater in the RG than in the UG (group of pregnant women who lived in Neuquén city), without previous history of pesticide exposure. Interestingly, when malnourished women, active and passive smokers, and alcohol consumers were excluded from the analysis for being considered confounding factors, the percentage of threatened miscarriage was still significantly greater in the RG, being two-fold greater than in the UG, suggesting that rural mothers experienced greater complications in their pregnancies for living close to areas where OPs are applied. Although threatened miscarriage has been associated with occupational exposure to pesticides and other contaminants (Park et al. 2017; Zhang et al. 1992), the relationship between threatened miscarriage and environmental pesticide exposure is understudied. Threatened miscarriage could be possibly related to underlying placental dysfunction (Davari-Tanha et al. 2008). Since in most cases of threatened miscarriage, bleeding originates from the placenta, we hypothesized that pregnancies complicated by a first-trimester threatened miscarriage could be at increased risk for other

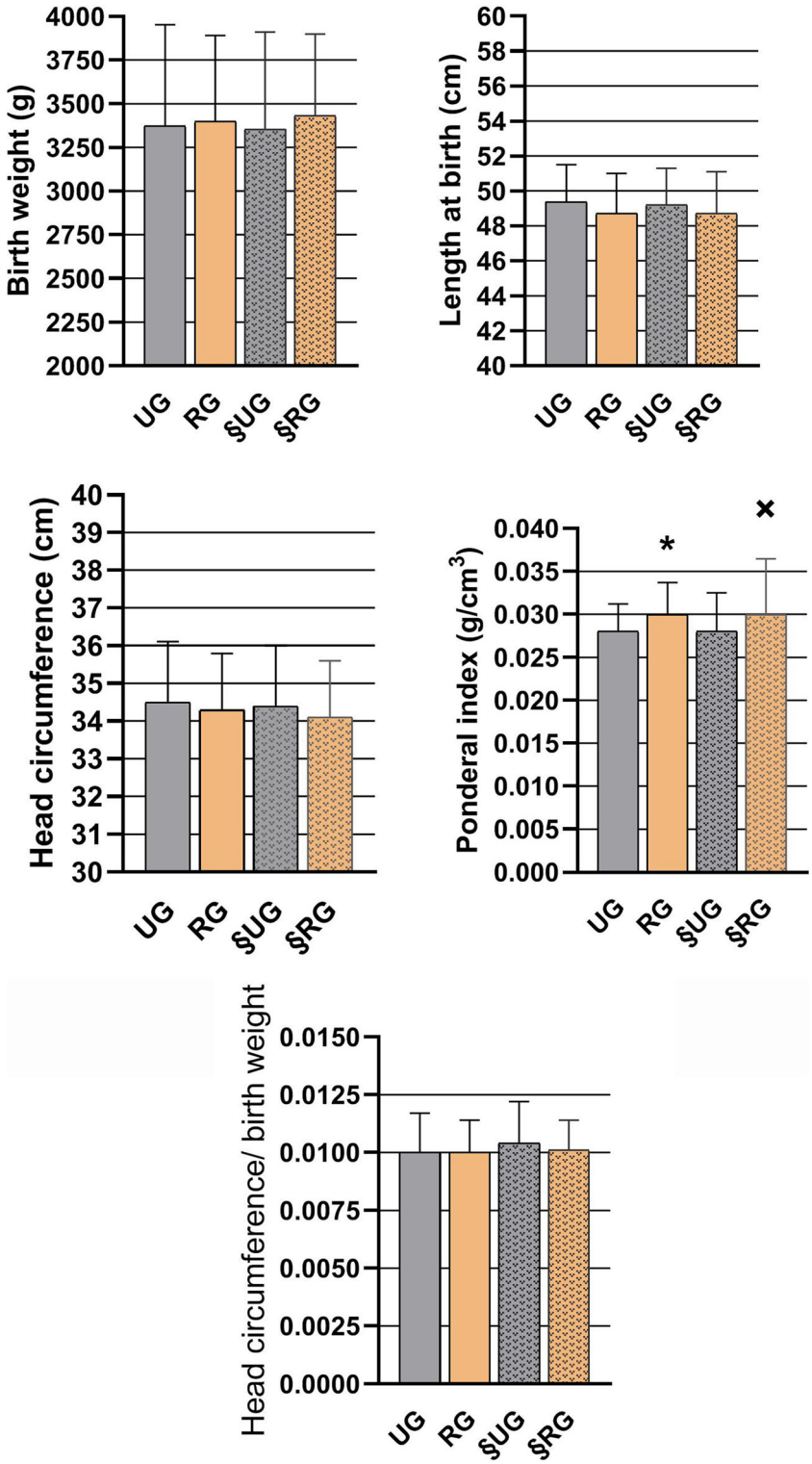


**Fig. 3** Newborn anthropometric measures. Results are expressed as means ± SD. UG: urban group; RG: rural group; §: data after excluding pregnant women with malnutrition, active and passive smokers, and alcohol consumers; missing values < 5%. *T*- test, *p < 0.05 UG (n = 358) and RG (n = 418), $^{x}$p < 0.05 §UG (n = 269) and §RG (n = 139)

placenta-related complications. In this context, it is of interest that, although placental calcification is a physiological phenomenon, in our study, placental calcifications were found only in the RG and not in the UG. There is currently a lack of consistent evidence on the clinical significance of placental calcification and its relationship with pregnancy outcome. Jamal et al. (2017) found that passive smoking was a predictor of placental calcification and concluded that it could be an alarm sign for placental dysfunction. However, in the present study, when we excluded the active and passive smokers from the analysis, the percentage of women with placental calcifications in the RG still remained at

**Table 2** Estimated newborn parameters' Z-scores values

| Parameter | §UG (Z-Score) (269) | §RG (Z-Score) (139) |
|---|---|---|
| Birth weight† (g) | 0.284 ± 0.922 | 0.347 ± 0.813 |
| Length at birth† (cm) | − 0.237 ± 1.037 | − 0.609 ± 1.164 ** |
| Head circumference (HC)† (cm) | − 0.063 ± 1.159 | − 0.391 ± 1.212 * |

Results are expressed as means ± SD; *UG*, urban group; *RG*, rural group; †corrected by sex and gestational age; §: data after excluding pregnant women with malnutrition, active and passive smokers, and alcohol consumers; missing values < 5%. *T*- test, **p < 0.01; *p < 0.05

17%. The potential association of pregnancy complications with placental parameters in this population is reinforced by our previous studies in the Alto Valle del Río Negro. In these studies, in term placentas collected in a rural population during the spraying period, we found alterations in steroidogenic function, lipid profiles, frequency of the expression of anti-inflammatory cytokines, and activities of enzymes related to detoxification and oxidative stress defense compared with placentas collected during the non-spraying period (Bulgaroni et al. 2013; Chiapella et al. 2014; Rivero - Osimani et al. 2016; Vera et al. 2012). In addition, in our previous studies performed in women residing in two rural localities of the Alto Valle del Río Negro, we recorded pregnancy complications in the third trimester (Santa- Cruz et al. 2020), being preterm premature rupture of membranes the pregnancy complication found in highest percentage in this rural population during the spraying period. In the present study, as we recorded pregnancy complications along the three trimesters in women living in most of the localities of the Valley, we managed to identify threatened miscarriage as a pregnancy complication associated with rural residence. Many investigators have reported increased incidence of preterm birth and low birth weight following threatened miscarriage. Similarly, it has been reported that the incidence of premature rupture of membranes is higher among patients with threatened miscarriage than among pregnant women

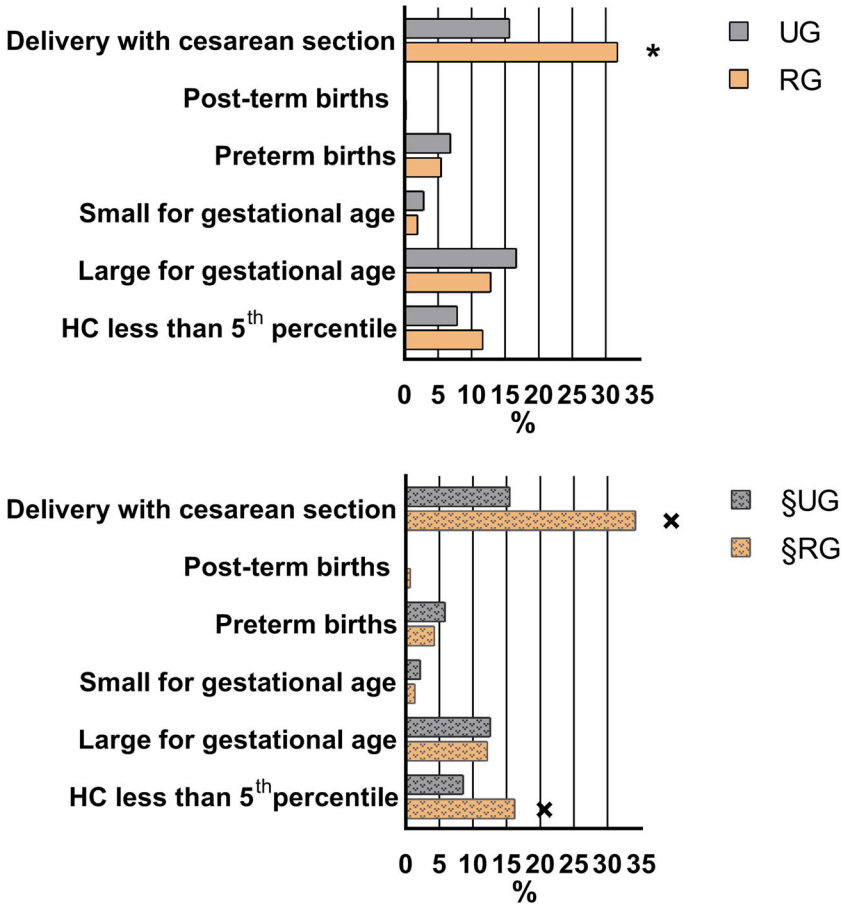


**Fig. 4** Mode of delivery and newborn parameters. UG: urban group; RG: rural group; §: data after excluding pregnant women with malnutrition, active and passive smokers, and alcohol consumers; HC: head circumference; missing values < 5%. $\chi^2$, *p < 0.05 UG (n = 358) and RG (n = 418), $^{x}$p < 0.05 §UG (n = 269) and §RG (n = 139)

without this complication (Buchmayer et al. 2004), and only few reports have found normal development following threatened miscarriage. However, in our study, premature rupture of the membranes was similar between the RG and the UG.

The exact cause of threatened miscarriage is debatable, although it is possible that more than one process is involved in the pathogenesis of this condition (Roshdy Ahmed et al. 2012). Our finding has important public health implications for successful pregnancies and the interpretation of adverse impacts of environmental chemical exposures on pregnancy. Deeper investigations are needed to understand the mechanism underlying the association between pesticide exposures and threatened miscarriage in this area.

Regarding miscarriage, it has been linked to serum levels of organochlorine pesticides (Longnecker et al. 2005; Venners et al. 2005) and pesticide exposure history data (Arbuckle et al. 2001). In areas with distinct exposure to pesticides, prevalence rates per 100,000 inhabitants for miscarriage have been found to be significantly greater than in those with low exposure (García et al. 2017). The association between miscarriage and exposure to pesticides may suggest that exposure to specific pesticides tends to damage the fetus or the fetus–placenta complex or cause chromosomal anomalies (Arbuckle et al. 2001; Harris et al. 2020). However, a study performed in Mexico in women chronically exposed to OPs (Blanco-Muñoz et al. 2013) found no association between maternal paroxonase (an enzyme involved in detoxification from OPs) polymorphisms and the risk of miscarriage. In our study, although the percentage of miscarriage was greater in the RG than in the UG, when pregnant women with malnutrition, active and passive smokers, and alcohol consumers were excluded from the analysis, no cases of miscarriage were observed in either group.

Regarding intrauterine fetal death, in contrast to that found by Bell et al. (2001), who found a slight association between residential proximity to agricultural OP applications and fetal death, our results showed no intrauterine fetal death in the pregnancies studied in both the RG and the UG.

Most studies so far performed to quantify *in utero* exposures have relied upon maternal urinary or blood concentration as a proxy. While these measurements are critical to quantify maternal exposure, they do not provide a direct measure of fetal exposure. Exposure to insecticides during pregnancy may increase the risk of adverse birth outcomes (Jaacks et al. 2019). In our study, newborn anthropometric parameters were adjusted by sex and gestational age prior to statistical comparisons in both groups. Our results showed that the newborns of women of the RG had a smaller BL, smaller HC and higher PI at birth than those of women of the UG, and that the percentage of newborns with HC below the 5th percentile was higher in the RG than in the UG after excluding pregnant women with malnutrition, active and passive smokers, and alcohol consumers from the analysis. The exclusion of cases of pregnant women that presented these features is supported by the literature. Studies have shown that mild to moderate alcohol consumption diminishes the at-birth HC of theoretically healthy newborns in a linear form (Ortega-García et al. 2012). A decrease in HC has been used as a biomarker of the effect of neurotoxicants and constitutes diagnostic criteria in fetal alcohol syndrome (Ervalahti et al. 2007). It is also well-acknowledged that a reduction in BW, LB, and HC is associated with smoking habits in pregnancy (Ortega-García et al. 2012; Vardavas et al. 2010; Raatikainen et al. 2007). Consistent with our results, a significant decrease in HC in infants of women exposed to pesticides has been associated with a low activity of the detoxifying enzyme paraoxonase 1 (Berkowitz et al. 2004), although Whyatt et al. (2004) observed no significant decrease in HC at birth related to OP concentrations in cord plasma samples. Additionally, a decreasing trend of HC and an increased risk of HC below the 5th percentile have been observed in infants of mothers residing in crop areas in France, where OPs are used (Petit et al. 2010). However, in another agricultural area of OPs applications, Eskenazi et al. (2004) found that HC at birth was positively correlated with the level of dialkyl phosphate metabolites in maternal urine in early pregnancy. Béranger et al. (2020) observed associations between maternal hair concentrations of various pesticides or metabolites, including OPs, CBMs, and NNTs, with BW, LB, and HC and suggested that prenatal exposure to pesticides belonging to distinct chemical families may influence birth outcomes. In contrast, Wang et al. (2012) found no associations for BW and LB with maternal OPs in urine, although, similarly to that found by Eskenazi et al. (2004), they showed decreased gestational duration for female fetuses.

Although BW, BL, and HC are not specific for a dysfunction or disease, these parameters are conventionally used to evaluate and predict intrauterine development and possible alterations in growth. It is noteworthy that HC at birth may be considered a predictor of the IQ and cognitive abilities (Lindley et al. 1999; Petit et al. 2010). Considerable evidence suggests that prenatal exposure to OPs contributes to child neurodevelopmental disorders (Sapbamrer and Hongsibsong 2019). Moreover, relationships between maternal residential proximity to agricultural use of neurotoxic pesticides and poorer neurodevelopment in children have been identified (Gunier et al. 2017) and close residential proximity to greenhouse floricultural crops has been associated with adverse neurobehavioral performance among children (Friedman et al. 2020).

In our study, the rural population studied (RG) consisted of pregnant women living close (within less than 5000 m) to intense use of pesticides. Although OPs are the principal type of pesticides used in this region, combined toxicity due to other pesticide groups such as CBMs and NNTs could

contribute to our results. Rappazzo et al. (2016) provided evidences of associations between residential exposure to agricultural pesticides and birth defects such as structural defects of several organs. In addition, Rull et al. (2006) found that maternal residential proximity within 1000 m of pesticide applications and exposure to OPs increased the risks of neural tube defects and anencephaly or bifid spine subtypes. In a retrospective study, Ling et al. (2018) found an increase in the risk of preterm birth among women living within 2000 m of agricultural application of pesticides (OPs, pyrethroids, and CBMs) during pregnancy, and their assessment revealed that exposure to pesticides was associated with preterm delivery but was rarely linked with term low BW. In addition, a meta-analysis of published data from the USA showed that pesticides were detected in house dust samples at a distance of 1000 m from treated agricultural fields (Deziel et al. 2017). However, the findings from the USA, where aerial spraying is common, may not be directly transferable to the situation in the Alto Valle del Río Negro, where ground-based spraying equipment is used in the season where the strongest winds occur, thus increasing the risk of exposure.

Fetal growth restriction, the main reason for low BW other than preterm birth, might result from transplacental oxygen and nutrient transport, hypoxia, oxidative stress, placental inflammation, and inhibition of placental growth hormones; these mechanisms may be influenced by toxic exposure to OPs and CBMs (Ling et al. 2018). Although in the present study we did not find much evidence for associations between term low BW and rural residence, we have previously reported altered placental oxidative stress parameters in this population (Chiapella et al. 2014). Thus, plausible mechanisms involving maternal, fetal, or placental units have yet to be identified to characterize the risk of the population of the Alto Valle del Río Negro.

We also found a significant association of the rural residence with the PI, which was increased in the RG. In this index, BW and LB are related. Newborns can be symmetrical or asymmetrical according to the PI. Symmetrical fetal development includes an appropriate relationship between BW and LB. Asymmetrical newborns with high PI have a relative greater weight than length, which is frequently taken as a measurement of obesity. Thus, the value of the PI is supplementary to the data of BW and LB. The PI at birth also predicts the body mass index and several diseases (Roje et al. 2004). In the present study, we corrected our data by sex and gestational age, important factors for the PI. Our results indicate that newborns of RG mothers were shorter relative to their weight at birth. Although BW did not differ between newborns of RG and UG mothers, an increased PI suggests fetal altered growth and organ maturation in those of RG mothers respect to those of UG mothers. The PI has been found to be a predictor of intrauterine growth restriction, but babies from RG mothers were not significantly smaller than those of UG mothers. The use of the PI curve for gestational age, together with other growth curves, improves the nutritional assessment of newborns (Fayyaz 2005).

It cannot be ruled out that the cause of the higher percentage of newborns delivered by cesarean section in RG with respect to UG, considering and not considering all participants, could be due to different characteristics and medical standards between the two areas.

This is the first multicenter study to identify the relationship between rural residence and pregnancy and newborn parameters covering a wide distribution of participants along the Alto Valle del Río Negro. An important strength of this study is the prospective design, as pregnant women were followed during pregnancy until delivery and their newborn's parameters were registered. This strengthens the interpretation of the findings, as we are sure that birth addresses reflect the residence of mothers over the entirety of pregnancy. Another strength of the present study is that estimating the exposure during the prenatal period, when individuals are highly vulnerable to environmental insults, allows early implementation of health controls for rural children. Additionally, this study complements other previous studies of our group, in which rural participants were examined comparing the spraying and non-spraying periods. Taken together, these studies may be applicable to other fruit production areas.

One limitation of this study is that women exposure to pesticides was estimated in the prenatal stage by residential proximity to fruit crops. Currently, there is no a standard to determine exposure to pesticides *in utero*. However, since exposure assessment by biomonitoring or environmental monitoring is often not feasible in large population studies, we did not rely on distance only, but took into account the results of our previous studies in the Alto Valle del Río Negro in the design of the study. Although there is some literature where other authors conducted exposure assessment by collecting urine multiple times, the design of our study attempted to be included in the normal pregnancy control protocol, without additional participation of the women beyond being recruited and the first interview, in order to avoid unintended impacts on participant's pregnancies. Another potential limitation of this study is that, when recording threatened miscarriage, the severity of vaginal bleeding was based on a subjective description by the patient. In addition, we did not collect information on potential routes of exposure to pesticides apart from whether or not the women lived in the rural communities, such as dietary intake. Despite these limitations, this study was undertaken based on a hospital-based study, with reliable information provided by the health personnel and also obtained from the medical record, and suggests that the risk of pregnancy complications and altered measures of birth outcomes could be associated with the pregnant women's residential

pesticide exposure estimated by proximity to fruit crops in the Alto Valle del Río Negro.

## Conclusion

Our results suggest that OPs applications may increase the risk of pregnancy complications and altered newborn parameters. Certainly, the magnitude of these associations should be interpreted cautiously and such associations need to be verified by means of further studies. While our results cannot prove a causal link between proximity to agrochemicals and pregnancy complications and birth outcomes, an association might provide clues to common factors shared by these variables. There is a clear need to understand this association to develop and optimize prevention strategies. Additionally, there is a need for studies regarding other associated biological effects to determine the extent of potential pregnancy and fetal alterations as well as possible long-term effects. Our results accentuate the need to establish monitorings in areas where there is residential proximity to fruit crops, recording biomarkers of exposure and effects obtained from different non-invasive matrices, as well as anthropometric data. The lack of a continuous follow-up on exposure and effects might lead to unfavorable decision-making concerning how to reduce the risk of pesticide drifting and runoff to nearby homes of vulnerable population groups.

**Abbreviations** BW, Birth weight; CBMs, Carbamates; HC, Head circumference; LB, Length at birth; NNTs, Neonicotinoids; OPs, Organophosphates; PI, Ponderal index at birth; RG, Rural group; UG, Urban group

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**Author contribution** AC: Methodology, Investigation, Data Curation, Resources
GA: Methodology, Investigation, Resources
NQ: Investigation, Data Curation
MCB: Investigation, Data Curation
SA: Investigation, Data Curation
GS: Formal analysis
GGM: Conceptualization, Writing - Review & Editing, Visualization, Supervision, Project administration, Funding acquisition
MGR: Conceptualization, Writing - Review & Editing, Visualization, Supervision, Project administration, Funding acquisition
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**Data availability** The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

## Declarations

**Ethics approval** The study protocol was approved by the ethical committee of the local Advisory Committee of Biomedical Research in Humans.

**Consent to participate** Amalia Cecchi, Gabriel Alvarez, Natalia Quidel, María Cecilia Bertone, Guillermo Sabino, and Gladis G. Magnarelli participated in the design, execution, and analysis of the paper entitled Residential proximity to pesticide applications in Argentine Patagonia: impact on pregnancy and newborn parameter, have seen and approved the final version, and that it has neither been published nor submitted elsewhere.

**Consent for publication** Not applicable.

**Competing interests** The authors declare no competing interests.

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