Pregnancy outcome following opioid exposure: A cohort study

Boris Fishman¹, Sharon Daniel¹², Gideon Koren³⁴⁵, Eitan Lunenfeld³⁶, Amalia Levy¹∗

¹ Department of Public Health, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel, ² Department of Pediatrics, Soroka Medical Center, Beer-Sheva, Israel, ³ Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel, ⁴ Motherisk Israel, Tel Aviv, Israel, ⁵ Maccabi Health Services, Tel Aviv, Israel, ⁶ Department of Obstetrics and Gynecology, Soroka Medical Center, Beer-Sheva, Israel

∗ lamalia@bgu.ac.il

Abstract

Introduction

Opioids constitute a cornerstone of pain relief treatment. However, opioid safety during pregnancy has not been well established. Recent studies reported an association between in utero opioid exposure and spina bifida.

Methods

In order to further evaluate the association of opioids exposure during pregnancy with adverse pregnancy outcomes, we conducted a large historical cohort by linking four databases: medications dispensations, births, pregnancy terminations for medical reasons and infant hospitalizations during the years of 1999–2009. Confounders that were controlled for included maternal age, ethnicity, maternal diabetes, smoking status, parity, obesity, year and folic acid intake. A secondary analysis for total major malformations and for spina bifida was performed using propensity score matching for first trimester exposure.

Results

Of the 101,586 women included in the study, 3003 were dispensed opioids during the first trimester. Intrauterine exposure to opioids was not associated with overall major malformations (adjusted odds ratio (aOR) 0.97, 95% CI 0.83–1.13), cardiovascular malformations (aOR = 0.89, 95% CI 0.70–1.13) other malformations by systems or spina bifida in particular. However, the risk for spina bifida among newborns and abortuses who were exposed to codeine was four times higher than that of the unexposed (aOR = 4.42, 95% CI 1.60–12.23). This association remained significant in a secondary analysis using propensity score matching. Third trimester exposure to opioids was not associated with low birth weight (aOR = 1.08, 95% CI 0.77–1.52), perinatal death (aOR = 1.38, 95% CI 0.64–2.99) and other adverse pregnancy outcomes.
Conclusions

These findings suggest that opioids exposure (as a homogenous group) is not a significant risk factor for overall major malformations. Exposure to codeine during the first trimester was found to be associated with increased risk of spina bifida. However, this finding was based on a small number of cases and need to be verified in future work.

Introduction

Opioid medications are commonly used by the general population and by women of reproductive age, particularly in developed countries[1–3]. Indeed, it has been shown that each year, 27–39% of reproductive age women in the US fill opioid prescriptions[4]. Opioids are mostly indicated for the treatment of pain and codeine is also prescribed as antitussive treatment.

Opioids have been shown to cross many surface barriers, including the placenta, eventually reaching fetal circulation[5,6]. Despite the extensive use of opioids by pregnant women, however, few studies have addressed the safety of fetal exposure during the first trimester of pregnancy. Although most of these studies did not find any association between opioids and congenital malformations[7–11], two recent, large case control studies found first trimester exposure to opioids to be associated with heart and neural tube defects (NTDs)[12,13]. Of potential importance, none of the studies published so far have included pregnancy terminations for medical reasons in their cohorts.

Our objective was to further evaluate the risk of adverse pregnancy outcomes following opioids and specifically propoxyphene and codeine exposure, during the first and third trimesters of pregnancy in a large, cohort study.

Materials and methods

Study population

We conducted a historical cohort study that included all women between the ages of 15 and 49 who were insured by the Clalit Health Maintenance Organization (CHMO). The CHMO insures more than 70% of reproductive age women in the Beer-Sheva district of Israel, which had 664,000 inhabitants in 2013. No differences were found between the population insured by the CHMO and the population insured by other health organizations in the southern district of Israel[14]. Of the deliveries in this district, 98% take place at Soroka Medical Center (SMC), the main regional hospital and the only one in this district.

The women included in our study attended SMC between the years of 1999 and 2009 to give birth or to undergo pregnancy termination due to confirmed or suspected malformations in the fetus. The risk for major malformations was previously shown to be increased among multiple gestations compared with singleton pregnancies[15]. Therefore, those pregnancies were excluded from this study. We also excluded fetuses with chromosomal aberrations, fetuses exposed to folic acid antagonists or antiepileptic medications (e.g., methotrexate and valproic acid) during the first trimester of the pregnancy and pregnancies of women who were known to use illicit drugs in the present or in the past (based on self-report during their hospitalization for birth or pregnancy termination or social services report).
Databases

To create the cohort, we combined four databases, three of which are computerized and based on information taken directly from original sources. The first computerized database is the SMC deliveries database, which contains information about all deliveries that took place at SMC, including maternal demographic information, parity, self-reported tobacco use during pregnancy, maternal medical conditions before and during pregnancy (e.g., pre-gestational diabetes mellitus and gestational diabetes mellitus), gestational age at delivery and delivery outcome. The second is the SMC pediatric hospitalizations database, which records information on all congenital malformations diagnosed up to one year of age and is encoded according to the international classifications of diseases, 9th revision (ICD-9). The third electronically recorded database contains information on drug dispensations, including date of dispensation and Anatomical Therapeutic Chemical (ATC) classification. A fourth database on pregnancy termination performed due to confirmed or suspected malformations in the fetus was manually created using the registry of the Committee for Termination of Pregnancies at SMC. This database includes maternal demographic information, date of termination, pregnancy age at the time of termination, and diagnoses of fetal malformations. The datasets were established in 2011 and were encoded and linked by the personal identification number assigned to every patient at SMC. All pregnancy records were successfully linked with newborn and children’s records. There was only one woman who had one record of a pregnancy in the cohort, in which we did not find any dispersion of any drug in the medication database. Since the southern district population comprises mostly religious Bedouin and Jewish population, the prevalence of smoking in our data was relatively low.

Study design

The exposed group included the newborns and fetuses of women to whom opioids were dispensed during the first 13 weeks of gestation. The prescribed opioids were: propoxyphene, codeine, tramadol, oxycodone and fentanyl. No other opioids were prescribed to the study’s participants. The first day of the last menstrual period was defined as the first day of pregnancy. The unexposed groups comprised the newborns and fetuses of all women who were not exposed to opioids during the first trimester. Because a relatively large number of exposures were of codeine (46%) and propoxyphene (49%) we performed sub-analyses for exposure to those specific medicines. Other opioids were not analyzed separately due to small number of exposures and a lack of statistical power.

We investigated the proportion of major malformations in newborns and fetuses after first trimester exposure to opioids and specifically to propoxyphene and codeine. We used the definition of major congenital malformations as defined by the Metropolitan Atlanta Congenital Defects Program of the Centers for Disease Control and Prevention[16–18]. In addition, we performed subclass analyses to investigate the risk of malformations by system and the specific malformations: central nervous system(CNS) malformations, including NTDs (ICD-9 codes: 740–742), NTDs (ICD-9 codes:740–741), cardiovascular system malformations (ICD-9 codes: 744–747), gastrointestinal tract system malformations (ICD-9 codes: 750–751), genitourinary system malformations (ICD-9 codes:751–752), musculoskeletal malformations (ICD-9 codes:753–754), spina bifida (SB) (ICD-9 code:741), anencephaly (ICD-9 code:740), and cleft palate and lip (ICD-9 code:749).

Furthermore, we investigated third trimester exposure to opioids in association with adverse birth outcomes. Those adverse outcomes might be associated with earlier gestational origin but third trimester in utero exposure to several drugs and chemicals was previously shown to affect fetal growth[19]. We investigated the risk among live neonates and stillbirths.
of the following adverse outcomes following third trimester (starting from week 29 of gestation) exposure to opioids and specifically to propoxyphene and codeine: perinatal death, low birth weight (<2500g), very low birth weight (<1500g), small for gestational age (SGA), and low Apgar score (<8) at 1 and 5 minutes after birth. We also analyzed the association between third trimester opioid exposure and neonatal abstinence syndrome (ICD9 code 779.5).

Malformations were detected in the neonatology unit by board-certified neonatologists and during hospitalizations of infants up to one year old in the SMC. For pregnancy terminations, malformations were diagnosed using ultrasound scans performed by gynecology and obstetrics physicians.

Statistical analysis

We used the SPSS software, version 17, to perform the statistical analyses (IBM SPSS; Somers, NY). Maternal characteristics of the exposed and unexposed groups were compared using the chi-square test for categorical variables and Student’s t-test for continuous variables. We tested multivariable logistic-regression models to determine whether intrauterine first trimester exposure to opioids was independently associated with congenital major malformations, malformations by system and specific malformations. The models were adjusted for the following maternal demographic characteristics and other known risk factors for congenital malformations: maternal age (in months), ethnic group (Bedouin Muslim or Jewish), self-reported tobacco use during pregnancy, pre-gestational diabetes mellitus (DM), obesity, nulliparity (yes/no). In addition to the confounders listed above, the models for CNS malformations, including NTD, were also adjusted for folic acid intake during the period starting three months before pregnancy to the end of the first trimester. We tested additional models to address the association of propoxyphene or codeine specifically with malformations as described above. In addition, to further validate our results, we performed a sub-analysis by examining the risk for major congenital malformations by the number of prescriptions dispensed during the first trimester of pregnancy.

We also performed multivariable logistic regression analyses to evaluate the association between third trimester exposure and other adverse pregnancy outcomes as mentioned (e.g., low birth weight, perinatal death). In addition to the potential confounders used in the models for first trimester exposure, for the third trimester models, we adjusted for gestational DM, congenital malformations and lack of pregnancy care, which was defined as three or fewer physician visits during pregnancy.

Propensity score matching (R, the MatchIt package) was performed in order to address possible selection bias i.e, the population of exposed pregnancies is different in characteristics from the non-exposed pregnancies population, such that exposed pregnancies are only compared with a group of non-exposed pregnancies that is similar in characteristics. This analysis was conducted for total major malformations following first trimester exposures to opioids overall and separately for codeine and propoxyphene. The variables that were used to create the propensity model were maternal age, ethnic group, tobacco use, diabetes mellitus (DM), obesity, nulliparity and the use of folic acid supplements. The matching was performed such that the propensity for drug exposure for every exposed pregnancy was as close as 0.1 standard deviations from the propensity of the matched unexposed pregnancies. The odds ratio (OR) and 95% confidence interval (CI) for total major malformations and for specific malformations found to be significant in preliminary analysis were calculated.

This study was approved by the local institutional ethics committee at Soroka Medical Center in accordance with the principles of the Declaration of Helsinki.

The SMC research ethics committee waived the requirement for informed consent because the data were obtained anonymously from medical files with no participation of patients.
Results

There were 100,491 singleton births and 1095 pregnancy terminations from 1999 to 2009 in SMC to mothers who did not use folic acid antagonists or anticonvulsants during the first trimester of their pregnancies. Overall, 3003 (3%) fetuses were exposed to at least one opioid medication during the first trimester, corresponding to 2,957 (2.9%) among the 100,491 live born infants and 46 (4.2%) of the 1095 pregnancy terminations. 1480 (1.5%) fetuses were exposed solely to propoxyphene and 1390 (1.4%) were exposed only to codeine without being exposed to other opioids during that period of the pregnancy, 50 pregnancies were exposed to tramadol, 7 to oxycodone and 2 to fentanyl. A total of 72 pregnancies were exposed to more than one opioid medication during the first trimester. A comparison of maternal characteristics between the exposed and unexposed groups is presented in Table 1.

The unadjusted and adjusted risks for total congenital malformations and congenital malformations by system following first trimester exposure to opioids as a group and specifically to propoxyphene and codeine are presented in Table 2 and Table 3, respectively. The

Table 1. Comparison of maternal characteristics of women unexposed to any of the opioids during the first trimester of pregnancy to women exposed to any of the opioids and to codeine or propoxyphene alone.

|                        | Not exposed to any of the opioids n = 98,583 (97%) | Exposed to any opioid n = 3003 (3%) | Exposed to Codeine n = 1390 (1.4%) | Exposed to Propoxyphene n = 1480 (1.5%) |
|------------------------|--------------------------------------------------|-----------------------------------|-----------------------------------|---------------------------------------|
| Age (mean±S.D)         | 28.6±5.8                                         | 30.26±6.1                         | 30.25±6.0                         | 30.08±6.1                             |
| Ethnicity (Bedouins)   | 63,298 (64.2%)                                   | 2111 (70.3%)                      | 822 (59.2%)                       | 1203 (81.3%)                          |
| Pre-gestational diabetes | 994 (1%)                                          | 51 (1.7%)                         | 23 (1.7%)                         | 25 (1.7%)                             |
| Smoking during pregnancy | 1910 (1.9%)                                      | 87 (2.9%)                         | 49 (3.5%)                         | 35 (2.4%)                             |
| Maternal obesity       | 273 (0.3%)                                       | 4 (0.1%)                          | 2 (0.1%)                          | 2 (0.1%)                              |
| Nulliparity (yes/no)   | 21,622 (22%)                                     | 419 (14%)                         | 219 (15.8%)                       | 183 (12.4%)                           |
| Folic acid intake      | 24,919 (25.3%)                                   | 1088 (36.2%)                      | 512 (36.8%)                       | 528 (35.7%)                           |

Abbreviations: SD, standard deviation

https://doi.org/10.1371/journal.pone.0219061.t001

Table 2. Unadjusted and adjusted risk (odds ratios (OR) and 95% confidence intervals (95% CI)) for congenital malformations after intrauterine exposure to opioids during the first trimester of pregnancy compared to unexposed.

| Major Malformations                  | Unexposed n = 98,583 (97%) | Opioids Exposed n = 3003 (3%) | Unadjusted OR (95% CI) | ^Adjusted OR (95% CI) | P    |
|--------------------------------------|----------------------------|-------------------------------|------------------------|-----------------------|------|
| Total                                | 5986 (6.1)                 | 178 (5.9)                     | 0.93 (0.73–1.19)       | 0.95 (0.82–1.11)      | 0.554|
| CVS                                  | 2462 (2.5)                 | 70 (2.3)                      | 0.90 (0.71–1.15)       | 0.89 (0.70–1.13)      | 0.326|
| CNS (NTD included)                   | 821 (0.8)                  | 24 (0.8)                      | 0.96 (0.64–1.44)       | 0.90 (0.59–1.37)      | 0.621|
| NTDs                                 | 162 (0.2)                  | 5 (0.2)                       | 1.01 (0.42–2.47)       | 1.13 (0.46–2.76)      | 0.793|
| Spina bifida                         | 72 (0.1)                   | 4 (0.1)                       | 1.82 (0.67–5.00)       | 1.82 (0.66–5.03)      | 0.246|
| Anencephaly                          | 72 (0.1)                   | 1 (0.01)                      | 0.81 (0.52–1.27)       | 0.57 (0.08–4.12)      | 0.577|
| Genitourinary                        | 805 (0.8)                  | 20 (0.7)                      | 0.81 (0.52–1.27)       | 0.80 (0.51–1.24)      | 0.315|
| Musculoskeletal                      | 1483 (1.5)                 | 51 (1.7)                      | 1.13 (0.85–1.50)       | 1.14 (0.86–1.51)      | 0.369|
| Gastrointestinal                     | 308 (0.3)                  | 11 (0.4)                      | 1.17 (0.64–2.14)       | 1.08 (0.59–1.98)      | 0.795|
| Cleft lip/palate                     | 134 (0.1)                  | 2 (0.1)                       | 0.49 (0.12–1.98)       | 0.47 (0.12–1.91)      | 0.293|

Abbreviations: OR, odds ratio; CVS, cardiovascular; CNS, central nervous system; NTDs, neural tube defects

^ Adjusted for: maternal age (in months), ethnic group (Bedouin Muslim or Jewish), self-reported tobacco use during pregnancy, pre-gestational diabetes mellitus, maternal obesity, nulliparity (yes/no) and folic acid intake (for models of CNS malformations, including NTD).
proportion of total major malformations in the total opioids group was 5.9% (178 out of 3003) compared to 6.1% (5986 of 98,853) in the unexposed group (crude odds ratio 0.93, 95% CI 0.73–1.19; aOR 0.95, 95% CI 0.82–1.11). No significant association was found between in utero propoxyphene and codeine exposure and major malformations (aOR 0.91, 95% CI 0.72–1.15 and aOR 0.95, 95% CI 0.77–1.18, respectively). In addition, no significant association was found between first trimester exposure to total opioids or to propoxyphene or to codeine specifically and total malformations and malformations of the cardiovascular, CNS, NTDs, gastrointestinal systems or malformations such as cleft lip and palate (Table 2 and Table 3).

An association was found between first trimester exposure to codeine and SB (crude OR 3.95, 95% CI 1.44–10.822; adjusted OR 4.42, 95% CI 1.60–12.23). However, no association was found in terms of exposure to total opioids or to propoxyphene.

**Sensitivity analyses**

In a sub-analysis, the risk for major congenital malformations was not increased among pregnancies with increasing number of prescriptions for opioids dispensed during the first trimester of pregnancy (aOR = 0.8 95% CI 0.62–1.01, aOR = 0.98, 95% CI 0.34–2.45 and aOR = 0.98, 95% CI 0.13–7.51) for pregnancies with one prescription, pregnancies with two prescriptions and pregnancies with three or more prescriptions during the first trimester, respectively).

---

**Table 3. Odds ratios for congenital malformations after intrauterine exposure to codeine or propoxyphene during the first trimester of pregnancy compared to unexposed.**

| Major malformations | Unexposed n = 98,583 (97%) n (%) | Codeine exposed n = 1390 (1.4%) n (%) | Adjusted OR (95% CI) P | Propoxyphene exposed n = 1480 (1.5%) n (%) | Adjusted OR (95% CI) P |
|---------------------|---------------------------------|--------------------------------------|------------------------|---------------------------------|------------------------|
| Total               | 5986 (6.1)                      | 75 (5.4)                             | 0.91 (0.72–1.15) 0.49   | 90 (6.1)                       | 0.95 (0.77–1.18) 0.75   |
| CVS                 | 2462 (2.5)                      | 31 (2.2)                             | 0.90 (0.63–1.28) 0.61   | 36 (2.4)                       | 0.89 (0.63–1.24) 0.53   |
| CNS (NTD included)  | 821 (0.8)                       | 16 (1.2)                             | 1.46 (0.89–2.41) 0.13   | 6 (0.4)                        | 0.45 (0.200–1.01) 0.05   |
| NTDs                | 162 (0.2)                       | 4 (0.3)                              | 2.04 (0.75–5.53) 0.16   | 1 (0.1)                        | 0.45 (0.06–3.21) 0.42   |
| Spina bifida        | 72 (0.1)                        | 4 (0.3)                              | 4.42 (1.60–12.23) <0.01 | 0                              | 0                      |
| Anencephaly         | 72 (0.1)                        | 0                                    | 0                      | 1 (0.1)                        | 1.16 (0.16–8.42) 0.88   |
| Genitourinary       | 805 (0.8)                       | 6 (0.4)                              | 0.53 (0.24–1.18) 0.13   | 13 (0.9)                       | 1.02 (0.59–1.78) 0.89   |
| Musculoskeletal     | 1483 (1.5)                      | 20 (1.4)                             | 1.00 (0.64–1.56) 0.96   | 25 (1.7)                       | 1.09 (0.73–1.63) 0.63   |
| Gastrointestinal    | 308 (0.3)                       | 3 (0.2)                              | 0.67 (0.21–2.09) 0.49   | 8 (0.5)                        | 1.52 (0.75–3.09) 0.24   |
| Cleft lip/palate    | 134 (0.1)                       | 1 (0.1)                              | 0.56 (0.08–4.04) 0.55   | 1 (0.1)                        | 0.44 (0.06–3.18) 0.41   |

Abbreviations: OR, odds ratio; CVS, cardiovascular; CNS, central nervous system; NTDs, neural tube defects

* Adjusted for: maternal age (in months), ethnic group (Bedouin Muslim or Jewish), self-reported tobacco use during pregnancy, pre-gestational diabetes mellitus, maternal obesity, nulliparity (yes/no) and folic acid intake (for models of CNS malformations, including NTD).

https://doi.org/10.1371/journal.pone.0219061.t003
In a secondary analysis using propensity score matching we matched pregnancies exposed to opioids during the first trimester of pregnancy with unexposed pregnancies at the ratio of 1:12. A total of 2999 pregnancies exposed to opioids overall were matched with 35,928 unexposed pregnancies, 1479 pregnancies exposed to propoxyphene were matched with 17,732 unexposed pregnancies and 1386 pregnancies exposed to codeine were matched with 16,590 unexposed pregnancies. In this analysis, no increased risk for total major malformations was found following first trimester exposure to opioids overall (OR 0.95, 95% CI 0.72–1.17), and specifically to propoxyphene (OR 0.96, 95% CI 0.76–1.19) and codeine (OR 0.92, 95% CI 0.72–1.17). In contrast, first trimester exposure to codeine was found significantly associated with SB (aOR 4.42, 95% CI, 1.60–12.23). Furthermore, no increased risk for major congenital malformations was found among pregnancies with increasing number of prescriptions dispensed during the first trimester of pregnancy. Our study did not show an association between exposure opioids during the third trimester of pregnancy and other adverse pregnancy outcomes, such as perinatal death.

Table 4. Odds ratios for adverse pregnancy outcomes (other than malformations) following third trimester intrauterine exposure to opioids, and specifically to codeine or to propoxyphene alone, compared to unexposed.

| Adverse outcome                          | Unexposed n = 98,849 (98.4%) | Opioids exposed n = 1638 (1.6%) | Adjusted OR (95% CI) | Codeine exposed n = 858 (0.9%) | Adjusted OR (95% CI) | Propoxyphene exposed n = 733 (0.7%) | Adjusted OR (95% CI) |
|------------------------------------------|------------------------------|---------------------------------|----------------------|---------------------------------|----------------------|-------------------------------------|----------------------|
| Birth weight < 2500 gr                   | 8194 (8.3)                   | 97 (6.0)                        | 1 (0.79–1.26)        | 48 (5.6)                        | 0.93 (0.67–1.29)     | 45 (6.1)                            | 1.08 (0.77–1.52)     |
| Birth weight < 1500 gr                   | 1286 (1.3)                   | 5 (0.3)                         | 1.20 (0.43–3.36)     | 2 (0.2)                         | 1.22 (0.28–5.37)     | 2 (0.3)                             | 1.03 (0.19–5.59)     |
| Perinatal death                          | 1209 (1.2)                   | 11 (0.7)                        | 1.0 (0.54–1.83)      | 4 (0.5)                         | 0.73 (0.27–1.96)     | 7 (1)                               | 1.38 (0.64–2.99)     |
| Apgar score ≤ 8 at 1 minute after birth  | 5617 (5.8)                   | 87 (5.4)                        | 0.98 (0.79–1.22)     | 46 (5.4)                        | 1.05 (0.77–1.42)     | 36 (5.0)                            | 0.85 (0.60–1.19)     |
| Apgar score ≤ 8 at 5 minutes after birth | 983 (1.0)                    | 15 (0.9)                        | 1.29 (0.77–2.16)     | 8 (0.9)                         | 1.38 (0.68–2.79)     | 5 (0.7)                             | 0.91 (0.37–2.20)     |
| Small for gestational age                | 5730 (5.7)                   | 73 (4.4)                        | 0.82 (0.65–1.04)     | 41 (4.8)                        | 0.85 (0.62–1.17)     | 30 (4.1)                            | 0.78 (0.54–1.13)     |

*Adjusted for: maternal age (in months), ethnic group (Bedouin Muslim or Jewish), self-reported tobacco use during pregnancy, pre-gestational or gestational diabetes mellitus, maternal obesity, nulliparity (yes/no), congenital malformations and lack of pregnancy care.

https://doi.org/10.1371/journal.pone.0219061.t004

In a secondary analysis using propensity score matching we matched pregnancies exposed to opioids during the first trimester of pregnancy with unexposed pregnancies at the ratio of 1:12. A total of 2999 pregnancies exposed to opioids overall were matched with 35,928 unexposed pregnancies, 1479 pregnancies exposed to propoxyphene were matched with 17,732 unexposed pregnancies and 1386 pregnancies exposed to codeine were matched with 16,590 unexposed pregnancies. In this analysis, no increased risk for total major malformations was found following first trimester exposure to opioids overall (OR 0.95, 95% CI 0.72–1.17), and specifically to propoxyphene (OR 0.96, 95% CI 0.76–1.19) and codeine (OR 0.92, 95% CI 0.72–1.17). In contrast, first trimester exposure to codeine was found significantly associated with SB (OR 3.69, 95% CI 1.04–10.45).

Analyses of third trimester exposure did not find any association between total opioids, propoxyphene or codeine exposure with other adverse pregnancy outcomes (Table 4). There were 15 neonates that were diagnosed with neonatal abstinence syndrome after birth. None of those 15 neonates was exposed to opioids during the third trimester of pregnancy.

**Discussion**

Opioids are one of the cornerstones of analgesia treatment in the general population and in pregnant women in particular. With half of all pregnancies unplanned, a potentially high proportion of pregnant women are exposed to this class of drugs. Our large historical study failed to show an association between exposure to opioids as a group in the first trimester and overall major malformations proportion or malformations by system. Separate analyses of codeine and propoxyphene exposure also failed to demonstrate most of these associations. However, exposure to codeine during the first 13 weeks of pregnancy was associated with SB (aOR 4.42, 95% CI, 1.60–12.23). Furthermore, no increased risk for major congenital malformations was found among pregnancies with increasing number of prescriptions dispensed during the first trimester of pregnancy. Our study did not show an association between exposure opioids during the third trimester of pregnancy and other adverse pregnancy outcomes, such as perinatal death.
Our study found a higher proportion of major malformations than the proportions that have been reported in previous reports from around the world [20] with several possible explanations for this finding. Our cohort also included pregnancy terminations done for medical reasons. Most of the pregnancies in our study were of women of Bedouin ethnicity, an ethnic group that mostly dwell in southern Israel. To the best of our knowledge no differences exist in the proportion of opioid use between Bedouins and the rest of the Israeli population. Nevertheless, Bedouins are from the lowest socio-economic status in Israel (according to the Israeli Central Bureau of Statistics) which is independently associated with increased risk for major congenital malformations [21,22]. Furthermore, Bedouins are known to have higher proportion of congenital malformations compared to Jews, due, in part, to the high prevalence of consanguinity [23,24].

Anti folic acid drugs are among the more common drugs known to be causing congenital malformations (Anti-epileptic medications in particular) in women of reproductive age [25], and therefore, pregnancies exposed to anti-folates were excluded from this study.

The findings of our study are consistent with the results of most previous studies addressing the safety of prenatal exposure to opioid medications and to codeine in particular [7–11]. A study by Kallen et al. [9] based on the Swedish Medical Registry did not find opioids, and specifically, codeine and dextropropoxyphene, to be associated with congenital malformations, including cardiac malformations. Similar to our results, the case control studies conducted by Broussard et al. [12] and Yazdy et al. [13] found an association between exposure to opioids and SB (unadjusted OR 2.0, 95% CI 1.3–3.2; aOR 2.2, 95% CI 1.1–4.1, respectively).

SB, one of the most prevalent NTDs, has a marked impact on the life of the newborn [26]. It is estimated that more than 70% of SB cases can be prevented by increasing maternal folic acid consumption [26]. Among the most studied teratogens believed to cause SB are anticonvulsants [27], but other medications [12,13] have also been suggested to cause this malformation. Previous animal studies detected endogenous opioid growth receptors in the CNS that may affect DNA synthesis in early fetal developmental stages [28,29] while others showed that in utero opioid exposure caused delayed development of the spinal cord [30,31], possibly due to increased neuroblast apoptosis [32]. These findings suggest a biological mechanism for the epidemiological association found in our study between codeine exposure during the first trimester of pregnancy and SB.

**Limitations and strengths**

A notable limitation of our study is that the databases used to build our cohort contained information about the dispensation of opioid medications to pregnant women, but we have no direct knowledge about patient adherence to the recommended treatment. However, other studies have shown that computerized databases of drug dispensation are highly correlated with drug use by the general population [33–35] and by pregnant women in particular [36]. Prescription records were also found to be a good source of data to study the association between drugs and congenital malformations [37]. To evaluate adherence to treatment, we compared the proportion of folic acid dispensation detected in our study to the proportion of folic acid consumption as reported by the Israeli Health Ministry [38] and found a similar proportion between the two. Another possible limitation is the misclassification of women as unexposed for those who have used opioids that were purchased prior to the examined period. Furthermore, the diagnosis of obesity was documented by the gynecologist on admission, hence, the proportion of obesity in our study is an underestimation of the proportion of obesity in the population. Nonetheless, the prevalence of adult obesity in Israel (20%) is lower compared with the prevalence in North America (36%) [39,40]. This study did not contain...
data on spontaneous abortions. Moreover, a potential association between exposure to opioids and pregnancy loss could potentially underestimate the association between opioid exposure and major malformations because fetuses might not survive long enough to be assessed for major malformations. Last, the opioids examined in this study are indicated for pain relief and for antitussive treatment. However, data regarding the specific indication of use was lacking. Nonetheless, we did not detect an association with adverse pregnancy outcomes, therefore the possibility of an indication bias is negligible.

Our study has several strengths. The study cohort was derived from SMC, the only hospital in the southern district of Israel, where practically all the births in this district take place. We adjusted our models for known risk factors for congenital malformations. Furthermore, this study included data regarding major malformations diagnosed on pregnancies that were terminated for a suspected malformation in the fetus. The inclusion of those observations was previously proved to prevent a bias towards the null hypothesis [41]. In addition, we excluded from our cohort fetuses and abortuses diagnosed with chromosomal abnormalities and those exposed in utero to folic acid antagonists or antiepileptic drugs, as these have been shown to increase the risk for major congenital malformations, particularly NTDs[25,26]. Finally, in order to overcome a possible selection bias regarding the exposure itself we performed a secondary analysis using propensity score matching for total major malformations following first trimester exposure to opioids overall and to propoxyphene and codeine specifically. Furthermore, a secondary analysis was also performed for the association between exposure to codeine and SB. Similar results were found. Although we tested the associations between opioids and various groups of major malformations, our results were not corrected for the number of comparisons. The p-value for the association between propoxyphene and Spina Bifida was lower than 0.001, therefore it is likely to remain significant after adjustment for multiple comparisons.

In conclusion, opioid medications as a group do not appear to be associated with increased risk of major malformations, malformations by systems, or specific malformations. Codeine and propoxyphene exposures were also not associated with total major malformations or with malformations by system. Our study supports previous studies suggesting an association between first trimester in utero codeine exposure and SB. However, the small number of cases among the exposed group in our study dictates the need for further research to clarify this association.

Author Contributions

Conceptualization: Gideon Koren, Amalia Levy.

Data curation: Sharon Daniel.

Formal analysis: Boris Fishman, Sharon Daniel, Eitan Lunenfeld.

Investigation: Boris Fishman.

Methodology: Boris Fishman, Sharon Daniel, Gideon Koren, Eitan Lunenfeld, Amalia Levy.

Project administration: Amalia Levy.

Supervision: Gideon Koren, Amalia Levy.

Writing – original draft: Boris Fishman, Sharon Daniel, Gideon Koren, Eitan Lunenfeld, Amalia Levy.
References

1. Kotecha MK, Sites BD. Pain policy and abuse of prescription opioids in the USA: A cautionary tale for Europe. Anesthesia. 2013; 68: 1210–1215. https://doi.org/10.1111/anae.12450 PMID: 24219249

2. Ponizovsky AM, Marom E, Zeldin A, Cherny NI. Trends in opioid analgesics consumption, Israel, 2000–2008. [Internet]. European journal of clinical pharmacology. 2011. pp. 165–8. https://doi.org/10.1007/s00228-010-0992-0 PMID: 21057940

3. Handal M, Engeland A, Rønning M, Skurtveit S, Furu K. Use of prescribed opioid analgesics and co-medication with benzodiazepines in women before, during, and after pregnancy: a population-based cohort study. Eur J Clin Pharmacol. 2011; 67: 953–60. https://doi.org/10.1007/s00228-011-1050-7 PMID: 21484468

4. Ailes EC, Dawson AL, Lind JN, Gilboa SM, Frey MT. Opioid Prescription Claims Among Women of Reproductive Age—United States, 2008–2012. MMWR. 2015; 64: 2008–2012.

5. J. De Castro JM, editor. Regional Opioid Analgesia. 1991.

6. Brunton LL, Laso JS PK, editor. Goodman & Gilman’s The Pharmacological Basis of Therapeutics. 12th ed. McGraw-Hill; 2011.

7. Nezvalova-Henriksen K, Spigset O, Nordeng H. Effects of codeine on pregnancy outcome: results from a large population-based cohort study. Eur J Clin Pharmacol. 2011; 67: 1253–61. https://doi.org/10.1007/s00228-011-1069-5 PMID: 21656212

8. Briggs G.G, Freeman R.K YS., editor. Drugs in pregnancy and lactation: a reference guide to fetal and neonate risk. 9th ed. Lippincott Williams & Wilkins; 2011.

9. Shaw GM, Malcoe LH, Swan SH, Cummins SK, Schulman J. Congenital cardiac anomalies relative to selected maternal exposures and conditions during early pregnancy. Eur J Epidemiol. 1992; 8: 757–60. Available: http://www.ncbi.nlm.nih.gov/pubmed/1426180 PMID: 1426180

10. Broussard CS, Rasmussen SA, Reefhuis J, Friedman JM, Jann MW, Riehle-Colarusso T, et al. Maternal treatment with opioid analgesics and risk for birth defects. Am J Obstet Gynecol. 2011; 204: 314.e1–11. https://doi.org/10.1016/j.ajog.2010.12.039 PMID: 21345403

11. Yazdy MM, Mitchell A a, Tinker SC, Parker SE, Werler MM. Periconceptional use of opioids and the risk of neural tube defects. Obstet Gynecol. 2013; 122: 838–44. https://doi.org/10.1097/AOG.0b013e3182a6643c PMID: 24084542

12. Rafaela C. National Insurance Institute of Israel, periodic survey [article in Hebrew] [Internet]. Jerusalem, Israel; 2012. Available: www.btl.gov.il/Publications/survey/Documents/seker_238.pdf (accessed 2019 March. 30)

13. Rasmussen SA, Oleny RS, Holmes LB, Lin AE, Keppler-Noreuil KM, Moore CA. Guidelines for case classification for the National Birth Defects Prevention Study. Birth Defects Research Part A—Clinical and Molecular Teratology. 2003. pp. 193–201. https://doi.org/10.1002/bdra.10012 PMID: 12797461

14. Zhao Y, Chen J, Wang X, Song Q, Xu HH, Zhang YH. Third trimester phthalate exposure is associated with DNA methylation of growth-related genes in human placenta. Sci Rep. Nature Publishing Group; 2016; 6: 1–8. https://doi.org/10.1038/s41598-016-0001-8

15. Centers for Disease and Control Prevention. Atlanta Congenital Defects Program [Internet]. [cited 12 Jun 2015]. Available: http://www.cdc.gov/ncbddd/birthdefects/MACDP.html

16. Rasmussen SA, Olney RS, Holmes LB, Lin AE, Keppler-Noreuil KM, Moore CA. Guidelines for case classification for the National Birth Defects Prevention Study. Birth Defects Research Part A—Clinical and Molecular Teratology. 2003. pp. 193–201. https://doi.org/10.1002/bdra.10012 PMID: 12797461

17. Zhao Y, Chen J, Wang X, Song Q, Xu HH, Zhang YH. Third trimester phthalate exposure is associated with DNA methylation of growth-related genes in human placenta. Sci Rep. Nature Publishing Group; 2016; 6: 1–8. https://doi.org/10.1038/s41598-016-0001-8

18. L Rynn, J Cragan, MD, A Correa, MD P. Update on Overall Prevalence of Major Birth Defects—Atlanta, Georgia, 1978–2005 [Internet]. 2008. Available: https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5701a2.htm (accessed 2019 March. 30)

19. Fan C, Yu D, Mo X, Feng Y, Wang S, Da M, et al. Maternal Socioeconomic Status and the Risk of Congenital Heart Defects in Offspring: A Meta-Analyses of 33 Studies. PLoS One. 2014; 9: e111056. https://doi.org/10.1371/journal.pone.0111056 PMID: 25347676
22. Vrijheid M, Dolk H, Stone D, Abramsky L, Alberman E, Scott JES. Socioeconomic inequalities in risk of congenital anomaly. Arch Dis Child. 2000; 82: 349–352. https://doi.org/10.1136/adc.82.5.349 PMID: 10799420

23. Sheiner E, Shoham-Vardi I, Sheiner EK, Mazor M, Katz M, Carmi R. Maternal factors associated with severity of birth defects. Int J Gynaecol Obstet. 1999; 64: 227–232. PMID: 10366043

24. Sheiner E, Shoham-Vardi I, Weitzman D, Gohar J, Carmi R. Decisions regarding pregnancy termination among Bedouin couples referred to third level ultrasound clinic. Eur J Obstet Gynecol Reprod Biol. 1998; 76: 141–146. https://doi.org/10.1016/S0301-2155(97)00178-4 PMID: 9481563

25. Matok I, Gorodischer R, Koren G, Landau D, Wiznitzer A, Levy A. Exposure to folic acid antagonists during the first trimester of pregnancy and the risk of major malformations. Br J Clin Pharmacol. 2009; 68: 956–62. https://doi.org/10.1111/j.1365-2125.2009.03544.x PMID: 20002091

26. Mitchell LE, Adzick NS, Melchionne J, Pasquariello PS, Sutton LN, Whitehead AS. Spina bifida. Lancet. 2004; 364: 1885–95. https://doi.org/10.1016/S0140-6736(04)17445-X PMID: 15555669

27. Källén B, Robert E, Mastroiacovo P, Martínez-Frias ML, Castilla EE, Cocchi G. Anticonvulsant drugs and malformations is there a drug specificity? Eur J Epidemiol. 1989; 5: 31–6. Available: http://www.ncbi.nlm.nih.gov/pubmed/2707392

28. Zagon IS, Verderame MF, McLaughlin PJ. The biology of the opioid growth factor receptor (OGFr). [Internet]. Brain research. Brain research reviews. 2002. pp. 351–76. Available: http://www.ncbi.nlm.nih.gov/pubmed/11890982

29. Zagon IS, Wu Y, McLaughlin PJ. Opioid growth factor and organ development in rat and human embryos. [Internet]. Brain research. 1999. pp. 313–22. Available: http://www.ncbi.nlm.nih.gov/pubmed/10519055

30. Nasiraei-Moghadam S, Sahraei H, Bahadoran H, Sadooghi M, Salimi SH, Kaka GR, et al. Effects of maternal oral morphine consumption on neural tube development in Wistar rats. Dev Brain Res. 2005; 159: 12–17. https://doi.org/10.1016/j.devbrainres.2005.06.012 PMID: 16054236

31. Kirby ML. Reduction of fetal rat spinal cord volume following maternal morphine injection. Brain Res. 1980; 202: 143–150. https://doi.org/10.1016/0006-8993(80)90649-6 PMID: 7427730

32. Nasiraei-Moghadam S, Kazeminezhad B, Dargahi L, Ahmadian I. Maternal oral consumption of morphine increases Bax/Bcl-2 ratio and caspase 3 activity during early neural system development in rat embryos. J Mol Neurosci. 2010; 41: 156–164. https://doi.org/10.1007/s12031-009-9312-6 PMID: 19936637

33. West SL, Savitz DA, Koch G, Strom BL, Guess HA, Hartzema A. Recall Accuracy for Prescription Medications: Self-report Compared with Database Information. 1995; 142: 1103–1112.

34. Johnson RE, Vollmer WM. Comparing sources of drug data about the elderly. J Am Geriatr Soc. 1991; 39: 1079–1084. PMID: 1753045

35. Ray WA, Griffin MR. Use of Medicaid data for pharmacoepidemiology. Am J Epidemiol. 1989; 129: 837–49. Available: http://www.ncbi.nlm.nih.gov/pubmed/2646920 https://doi.org/10.1093/oxfordjournals.aje.a115198 PMID: 2646920

36. De Jong Van Den Berg LTW, Feenstra N, Sorensen HT, Cornel MC. Improvement of drug exposure data in a registration of congenital anomalies. Pilot-study: Pharmacist and mother as sources for drug exposure data during pregnancy. Teratology. 1999; 60: 33–36. https://doi.org/10.1002/(SICI)1096-9926(199907)60:1<33::AID-TERA9>3.0.CO;2-X PMID: 10413337

37. de Jonge L, de Walle HEK, de Jong-van den Berg LTW, van Langen IM, Bakker MK. Actual Use of Medications Prescribed During Pregnancy: A Cross-Sectional Study Using Data from a Population-Based Congenital Anomaly Registry. Drug Saf. Springer International Publishing; 2015; https://doi.org/10.1007/s40264-015-0302-z PMID: 26041497

38. ICDC. Health Status in Israel 2010. In: Ministry of Health, Israel. 2010.

39. T F. No Title CDC Health Disparities and Inequalities Report—United States, 2011 [Internet]. 2011. Available: https://www.cdc.gov/mmwr/pdf/other/su6001.pdf (accessed 2019 March. 30)

40. Lev B R. Health Behaviors-Prevention and Treatment of Obesity [Internet]. Jerusalem, Israel; 2011. Available: https://www.health.gov.il/PublicationsFiles/Obesity_prof_en.pdf (accessed 2019 March. 30)

41. Levy A, Matok I, Gorodischer R, Sherf M, Wiznitzer A, Uziel E, et al. Bias toward the null hypothesis in pregnancy drug studies that do not include data on medical terminations of pregnancy: the folic acid antagonists. J Clin Pharmacol. 2012; 52: 79–83. https://doi.org/10.1177/0091270010390806 PMID: 21343345