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ORIGINAL RESEARCH ARTICLE

A Retrospective Cohort Study of Obstetric Outcomes in Opioid-Dependent Women Treated with Implant Naltrexone, Oral Methadone or Sublingual Buprenorphine, and Non-Dependent Controls

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Abstract

Background Opioid pharmacotherapies play an important role in the treatment of opioid-dependent women; however, very little is known about the safety of naltrexone in pregnant patients.

Objective This study examined the obstetric health of opioid-dependent women who were treated with implant naltrexone during pregnancy, and compared them with women treated with methadone and/or buprenorphine and a cohort of non-opioid-dependent controls.

Methods Women treated with implant naltrexone, oral methadone or sublingual buprenorphine between 2001 and 2010, along with a cohort of age-matched controls, were linked with records from midwives, hospital and emergency departments (EDs) and the death registry to identify pregnancy and health events that occurred during pregnancy and in the post-partum period.

Results Overall rates of pregnancy loss (requiring hospital or ED attendance) were significantly elevated in naltrexone-treated women compared with buprenorphine-treated women ($p = 0.018$) and controls ($p < 0.001$); however, they were not statistically different to methadone-treated women ($p = 0.210$). Birth rates in women on naltrexone implant treatment were significantly higher than in all three comparison groups ($p < 0.001$). Rates of hospital and ED attendance during pregnancy in the naltrexone-treated women were not statistically different to those of either the methadone or buprenorphine groups, and neither were overall complications during pregnancy and labour. Overall rates of complications during pregnancy were significantly higher in the naltrexone-treated women than in the controls.

Conclusion Opioid-dependent women treated with naltrexone implant had higher rates of birth than the other three groups (methadone- or buprenorphine-treated women, or age-matched controls). Overall rates of complications during pregnancy were elevated in naltrexone-treated women when compared with the control group, but were generally not significantly different to rates in methadone- or buprenorphine-treated women.

Key Points

Rates of birth are high in naltrexone-treated women.

Rates of morbidity in pregnant naltrexone-treated women are generally not significantly different to rates in methadone- and buprenorphine-treated women.

1 Introduction

Naltrexone is an opioid antagonist used in the treatment of opioid dependence. While pharmacologically effective, the clinical efficacy of naltrexone has been problematic due to non-compliance issues with the oral formulation [1]. The development of sustained-release naltrexone preparations

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to overcome non-compliance has resulted in superior clinical efficacy [2]. However, the use of these preparations has generated a number of clinical questions with regards to safety outcomes in pregnancy and fertility.

With sustained-release naltrexone preparations becoming more readily available, concerns have arisen regarding the potential for women to become pregnant on treatment. Some clinical observations suggest that the incidence of pregnancy may increase following naltrexone treatment, potentially due to the cessation of opioids (and thus the restoration of normal menstruation), increased sex drive, re-establishment of relationships and increased self-care (nutrition, hygiene, etc.). Alternatively, the increased incidence may be directly attributable to naltrexone, with naltrexone having been shown to simulate luteinising hormone and follicle-stimulating hormone during the early follicular phase of the menstrual cycle [3, 4]. As such, clinically, naltrexone has been found to induce ovulation and reinstate normal menstruation in non-opioid-dependent women with weight loss-associated and hypothalamic amenorrhea, and polycystic ovarian disease [5–7]. Notwithstanding, rates of pregnancy and birth in naltrexone-treated opioid-dependent women have not been reported.

Increased rates of pregnancy are a concern as the effects of naltrexone on the developing fetus and the pregnant mother are not fully understood [8]. Clinically, the use of naltrexone has only been presented in a small number of case studies and a brief report on a case series [9–11], with generally unremarkable outcomes. However, the scope of these studies has generally been limited to basic neonatal outcomes (birth weight, gestation length, Apgar scores). Similarly, non-clinical studies of the use of naltrexone in pregnancy have focused on neonatal health rather than maternal health [12].

In addition to concerns regarding the direct effects of naltrexone on maternal and fetal safety, concerns have also arisen about the requirement for opioid withdrawal prior to induction onto naltrexone potentially resulting in intrauterine abstinence syndrome, which may have detrimental effects on the fetus [13, 14]. Similarly, concerns have been raised regarding the use of oral naltrexone during pregnancy and the potential for treatment dropout, relapse and opioid overdose, possibly resulting in both maternal and fetal harm [10]. Additionally, high rates of fatal and non-fatal opioid overdose have been observed in non-pregnant opioid-dependent patients following the cessation of oral naltrexone treatment [15, 16]. Additionally, the nature of the depot preparations can make cessation difficult if a patient becomes pregnant during their period of exposure, and thus patients may have to remain on treatment for a predefined period.

The aim of this study is to examine rates of birth in women treated with a sustained-release naltrexone preparation (an implant) and their health during pregnancy, labour, delivery and post-partum, and compare it with patients treated with methadone or buprenorphine and non-dependent controls.

2 Methods

2.1 Subjects

The study cohort included all women treated with implant naltrexone (manufactured by Go Medical Industries Pty. Ltd., Subiaco, WA, Australia) who were treated in Western Australia (WA) between January 2001 and December 2010. Women treated with implant naltrexone were identified from clinic treatment records from a not-for-profit drug and alcohol clinic located in Subiaco, WA. This clinic was the sole provider of this implant formulation in WA at the time. Pregnancies in which the neonate was exposed to naltrexone for more than 30 days were included in the study. The period of exposure following implant naltrexone treatment was considered to be 182 days based on pharmacokinetic and efficacy data [2, 9, 17].

The study also included women treated with oral methadone and sublingual buprenorphine (both buprenorphine alone [Subutex®; Reckitt Benckiser Healthcare (UK) Ltd., Hull, UK] and in combination with naloxone [Suboxone®; Reckitt Benckiser Healthcare (UK) Ltd.]) in WA between January 2001 and December 2010. Women treated with methadone and/or buprenorphine were identified via the Monitoring of Drug of Dependence System (MODDS). MODDS is maintained by the WA Department of Health and contains notifications of the prescribing of all schedule 8 and 9 drugs of dependence in WA. Prescribing data obtained from MODDS provided monthly records indicating whether or not the patient had received either treatment in that month. MODDS records were linked to authorisation records, which contained the date on which the patient was authorised to commence treatment and the date on which treatment was terminated. On occasions where the authorisation or termination date were absent, the 15th of the month was used as the commencement date and the last day of the month was used for the termination date. Pregnancies in which the neonate was exposed to methadone and buprenorphine for at least 60 days were included in the study. This period was twice that of naltrexone due to potential inaccuracies in the commencement and termination dates. For methadone, the group was limited to women treated for the first time between January 2001 and December 2010 as a result of the way the data were extracted.

A cohort of age (5-year age bracket)-matched non-opioid-dependent controls (1:1 ratio with opioid-dependent patients) was selected from the electoral roll by the Data Linkage Branch to act as a control group. The control group was matched against opioid treatment records to ensure that included individuals had not previously received an opioid pharmacotherapy.

All women included in the study were aged between 18 and 45 years at the time of first treatment and at the time of childbirth. Treatments that occurred after a patient reached 45 years of age were excluded from analysis (no births were observed in women 45 years or over).

2.2 Data Linkage

The cohorts were linked by the Data Linkage Branch with Hospital Morbidity Data Collection (HMDC), Emergency Department Data Collection (EDDC) and WA Death Registry (WADR) to identify pregnancies that had resulted in maternal or fetal losses. Additionally, the women were linked with the Midwives Notification System (MNS) to identify pregnancies that resulted in either a live or stillborn neonate of at least 20 weeks' gestation or, where gestation was unknown, at least 400 g birth weight. Women who were identified as having given birth were then re-linked against the HMDC and EDDC to ascertain inpatient hospital admissions and ED attendances that had occurred during the pregnancy and post-partum period. ED data were only available from 1 January 2002; thus, rates of ED attendance were calculated for women who conceived after this time. These women were also linked against the WA Notifiable Infectious Diseases Database (WANIDD) to determine rates of hepatitis C virus (HCV) in the pregnant women. Table 1 summarises the dataset used and the source of key variables included in the study.

2.3 Outcomes

The study set out to examine the following outcomes in relation to pregnant opioid-dependent women treated with implant naltrexone compared with opioid-dependent women treated with methadone and buprenorphine, and non-opioid-dependent controls:

- Crude birth rates.
- Crude and type-specific rates of pregnancy loss (resulting in hospital or ED attendance).
- Crude rates of hospital admissions during pregnancy and the post-partum period, as well as type-specific (opioid, non-opioid drug, mental health and obstetric) and trimester-specific admission rates.
- Crude rates of ED attendance during pregnancy and the post-partum period, as well as type-specific (opioid, non-opioid drug, mental health and obstetric), trimester-specific and severity (as indicated by triage categories) rates of ED attendance.
- Rates of type-specific complications during pregnancy, labour and delivery as reported at birth.

2.4 Data Analysis

Crude birth rates for each cohort were calculated for neonates conceived on treatment (as calculated from estimated length of gestation at birth) and expressed per thousand patient-years (ptpy). Rates of birth in the naltrexone cohort were compared with methadone, buprenorphine and the controls using univariate generalised estimating equations (GEEs), with a negative binomial distribution and a log link function. GEEs were selected for this analysis as opioid-dependent participants may have received more than one treatment, which could be accounted for in the model.

Rates of pregnancy losses identified from hospital and ED records using assigned ICD-10-AM (*International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification*) codes and Australian Classification of Health Interventions (ACHI) codes were expressed ptpy. Additionally, rates of type-specific pregnancy losses were calculated, including ectopic pregnancy (ICD-10-AM: O00), hydatidiform mole (O01), other abnormal product of conception (O02), spontaneous abortion (O03), medical abortions (O04/ACHI: 90461-00/90462-00/90463-00/90463-01) and other or unspecified abortion (O05–06). As per rates of birth, rates of pregnancy loss were compared using a univariate GEE, which allowed for women to be included in more than one treatment group.

For outcomes associated with pregnancy and childbirth, pregnancies in which the neonates were exposed to two or more treatments were excluded from analysis. Additionally multiple births (twins and triplets) were removed. For women who had more than one birth during follow-up, only one pregnancy was included in the study. Due to the sample size, priority was given to naltrexone pregnancies, followed by buprenorphine and then methadone. Where applicable, the first recorded pregnancy was also used in preference to subsequent pregnancies (Fig. 1).

For each pregnancy, maternal demographic information (smoking status, HCV status, maternal age at birth, number of previous pregnancies and socio-demographic status) was compared using univariate generalised linear models, with the exception of socio-demographic status, which was analysed using a Wilcoxon signed rank tests due to its unsuitable distribution. Socio-economic status was taken from assigned Socio-Economic Indexes for Areas (SEIFA)

Table 1 Data sources

Data source	Abbreviation	Details
Naltrexone treatment records		Implantation dates
Monitoring of Drugs of Dependence System	MODDS	Monthly methadone/buprenorphine dispensing, medication type, dose
Authorisation records		Commencement and cessation date of methadone and buprenorphine treatment
WA Electoral Roll		Selection of matched controls
Midwives Notification Scheme	MNS	Identification of births, includes data on pregnancy and labour complications, use of anaesthetic, estimated gestation, previous pregnancies, maternal age, SEIFA
WA Death Registry	WADR	Maternal deaths during pregnancy and the post-natal period
Hospital Morbidity Data System	HMDS	Pregnancy loss and terminations that occurred in hospital
		Hospitalisations during pregnancy and the post-natal period
Emergency Department Data Collection	EDDC	Pregnancy loss that resulted in ED presentation
		ED attendances during pregnancy and the post-natal period
WA Notifiable Infectious Diseases Database	WANIDD	Hepatitis C diagnosis

ED emergency department, *SEIFA* Socio-Economic Indexes for Areas (0 – lowest socio-economic area of residence, 10 – highest socio-economic area of residence), *WA* Western Australia

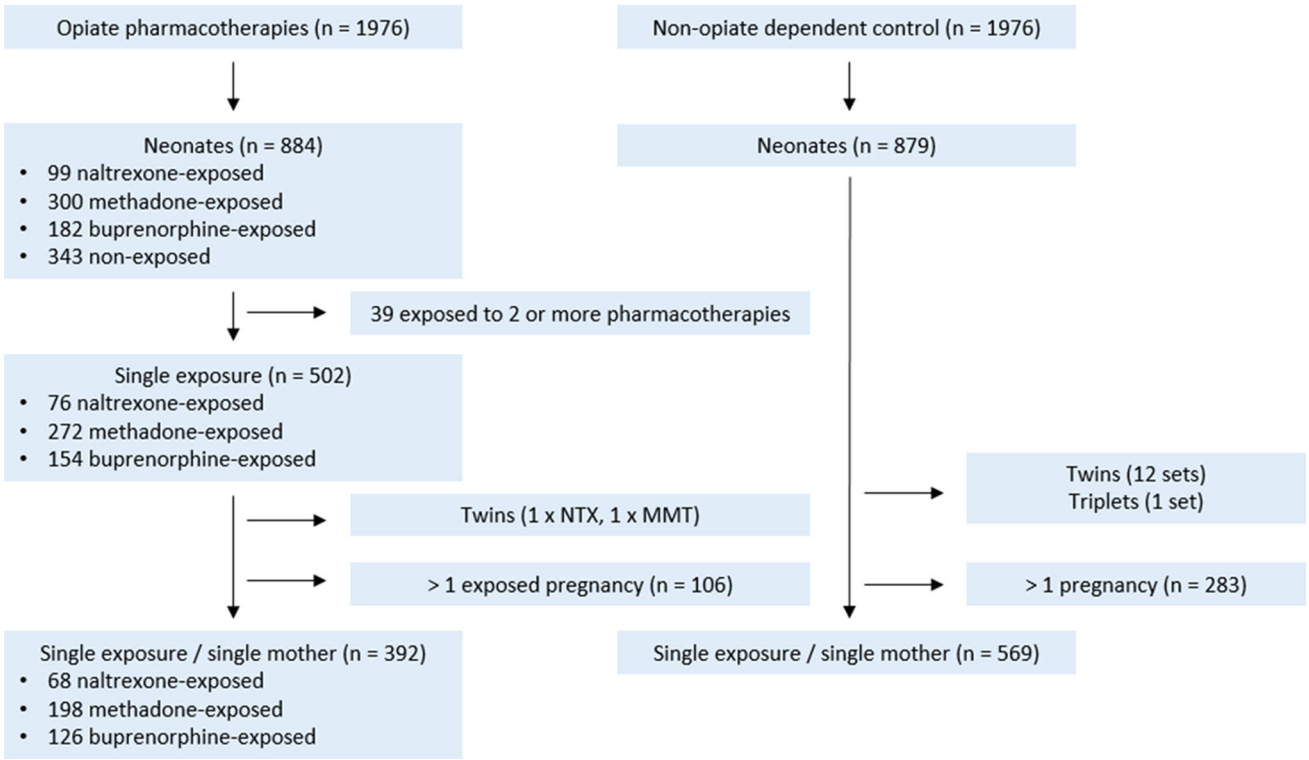

Fig. 1 Flow chart of women and their exposed neonates included in the study. *MMT* methadone maintenance treatment, *NTX* naltrexone

scores and rankings. The SEIFA scores are calculated by combining information collected in the 5-yearly Census of Population and Housing. The SEIFA Index of Relative Socio-Economic Advantage/Disadvantage (IRSEAD) for 2006 was used as a crude indicator of socio-economic status. IRSEAD data were used in the form of deciles, with suburbs ranked 1 having the lowest 10% of scores for census collection districts in Australia, while those ranked 10 had the top 10% of scores [18].

Rates of hospital admission and ED attendance during pregnancy and the post-partum period (first 42 days following birth) in the naltrexone cohort were compared to the three

other groups using generalised linear models with a negative binomial distribution and a log link function. For overall rates, a multivariate analysis was performed, taking into account smoking status, maternal age at birth, number of previous pregnancies and socio-demographic status. Univariate analysis was carried out examining rates of hospital admission and ED attendance within each trimester and the post-partum period (first 42 days following birth), as well as rates of events with an opioid poisoning (ICD-10-AM: T40.0–40.4), non-opioid drug and alcohol poisoning (T36–39.9, T40.5–51), non-drug mental health (F0–10/F20–99) and pregnancy/childbirth diagnosis (O00–99). For hospital admission, both primary and additional diagnoses were used, while only a primary diagnosis was available for ED attendance (however, in many cases no diagnosis was available for ED data). Rates of ED attendance were also divided into severity of attendance using assigned codes from the Australasian Triage Scale [19]. An ED attendance allocated a triage scale code of 1 is indicative of an immediately life-threatening condition, while a code of 5 is considered of minimal urgency.

Multivariate linear and logistic regression was use to compare overall rates of complications during pregnancy and delivery. Multivariate analysis factored in smoking status, maternal age at birth, number of previous pregnancies and socio-demographic status. Univariate analysis was used for examining the type-specific complications and other variables associated the pregnancy and delivery.

A critical p value of 0.05 was used, with no adjustment made for multiple comparisons. Data analysis was conducted using STATA/IC^{TM} 12.1 (STATACorp LLC, College Station, TX, USA).

2.5 Ethics

This study protocol was approved by the Department of Health Human Research Ethics Committee (2012/63) and the University of Western Australia Human Research Ethics Committee (RA/4/1/1864).

3 Results

3.1 Demographics

The study included 1976 opioid-dependent women treated with implant naltrexone, methadone and/or buprenorphine and 1976 age-matched controls (Table 2). Women moved readily between the three treatments, with 676 (34.2%) treated with naltrexone, 1204 (60.9%) treated with methadone and 1178 (59.6%) treated with buprenorphine. Following their initial treatment, opioid-dependent participants were followed up for an average of 7.3 ± 3.0 years, while control participants were followed up for an average of 7.4 ± 3.0 years.

3.2 Birth Rates

Birth rates in women who conceived while on naltrexone treatment were significantly higher than in those on methadone (relative risk [RR] 0.49, 95% confidence interval [CI] 0.37–0.63), buprenorphine (RR 0.53, 95% CI 0.40–0.71) and the controls (RR 0.49, 95% CI 0.38–0.63) (Table 2). Of the exposed pregnancies, 83.8% of the naltrexone-, 68.3% of the methadone- and 79.7% of the buprenorphine-treated women conceived while on treatment, while the remainder were treated after becoming pregnant.

3.3 Maternal Death and Pregnancy Loss

No maternal fatalities were observed during pregnancy or the post-natal period.

Overall rates of abortive outcomes (requiring hospital admission or ED attendance) in naltrexone-treated women were not significantly different to women treated with methadone (RR 0.80, 95% CI 0.56–1.14) but were higher than those treated with buprenorphine (RR 0.63, 95% CI 0.43–0.92) and the control group (RR 0.37, 95% CI 0.26–0.51). Elevated rates in the naltrexone cohort were primarily associated with elevated rates of ectopic pregnancies and medical abortions (Table 3).

3.4 Demographics of Pregnant Women at Birth (Single Exposure)

Of the 1976 women treated with an opioid pharmacotherapy, 68 naltrexone-, 198 methadone- and 126 buprenorphine-exposed infants were born with exposure to a single pharmacotherapy and unique mother (Fig. 1). Characteristics of women treated with naltrexone during pregnancy (single exposure) were similar to those in both methadone- and buprenorphine-treated women (Table 4). As compared with the control women, naltrexone-treated women were more likely to be younger (26.8 vs. 29.8 years), had more previous pregnancies (2.4 vs. 1.2 pregnancies), were less likely to be married or in a de facto relationship (52.9 vs. 92.3%), were of a lower socio-economic status (SEIFA 4.9 vs. 5.9), and were more likely to have smoked during pregnancy (70.2 vs. 13.0%) and been diagnosed with HCV (52.9 vs. 0.4%).

3.5 Pregnancy Complications: Hospital Admission and Emergency Department Attendance

Overall rates of hospital attendance during pregnancy (including the post-natal period) in the naltrexone cohort were not significantly higher than those in either of the three comparison groups. There was no significant difference

Table 2 Rates of birth and characteristics of women treated for opioid dependence with implant naltrexone compared with women treated with methadone or buprenorphine and a cohort of controls

Rates of birth/characteristics	Naltrexone	Methadone	Buprenorphine	Control
No. of women[a]	676	1204	1178	1976
Treatment start age (years)	29.0 ± 6.6	29.1 ± 6.7	29.5 ± 6.6	28.8 ± 6.9[b]
Time on treatment/participant (years)	1.1 ± 0.8	2.8 ± 2.7	2.0 ± 2.4	NA
No. of births[c]	99	300	182	879
No. conceived on treatment	83	205	145	NA
Crude birth rates (PTPY)	116.2	60.5*	62.6*	60.7*

NA not applicable, *PTPY* per 1000 patient years

* $p < 0.001$ (compared with the implant naltrexone group)

[a] Participant may have been treated with more than one opioid pharmacotherapy

[b] In the control group, start age was based on the corresponding start date of their matched case

[c] Includes neonates with exposure to more than one pharmacotherapy, multiple births (i.e. twins and triplets) and subsequent births

Table 3 Rates of pregnancies with abortive outcomes requiring emergency department attendance or hospital admission in opioid-dependent women treated with naltrexone ($n = 676$) compared with women treated with methadone ($n = 1204$), buprenorphine ($n = 1178$) and non-opioid-exposed controls ($n = 1976$), expressed per 1000 patient-years

Outcome	Naltrexone	Methadone	Buprenorphine	Control
Ectopic pregnancy	5.6	0.9*	1.3	1.3**
Hydatidiform mole	0.0	0.6	0.0	0.1
Other abnormal product of conception	5.6	2.7	4.3	4.8
Spontaneous abortion	4.2	13.0	3.5	5.2
Medical abortion[a]	43.4	30.1	25.0*	9.0***
Other/unspecified abortion	0.0	0.6	0.9	0.1
Failed abortions	0.0	0.0	0.0	0.0
Pregnancies with abortive outcomes	58.8	47.8	34.9*	20.7***

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ (compared with the implant naltrexone group)

[a] Includes both elective and therapeutic abortions

Table 4 Maternal demographics and characteristics of women treated with implant naltrexone during pregnancy compared with those treated with methadone or buprenorphine and control women

Maternal demographics/characteristics	Naltrexone	Methadone	Buprenorphine	Controls
No. of mothers/pregnancies	68	198	126	569
Marital status (%)				
Never married	45.6	36.4	42.1	5.8**
Married (include de facto)	52.9	56.6	52.4	92.3**
Divorced/separated/widowed	1.5	3.0	4.0	1.4
Unknown	0.0	2.5	1.6	0.5
SEIFA	4.9 ± 3.0	4.5 ± 2.5	4.4 ± 2.7	5.9 ± 2.5*
Diagnosed with hepatitis C (%)	52.9	63.1	60.3	0.4**
Previous pregnancies (range)	2.4 (0–15)	2.6 (0–10)	2.2 (0–7)	1.2 (0–18)**
Maternal age at birth (range)	26.8 (19–40)	27.8 (18–42)	27.9 (19–40)	29.8 (20–43)**
Smoked during pregnancy (%)	70.2	76.5	75.8	13.0**
Gender of neonates (% male)	47.1	58.1	54.8	50.4
Estimated gestation of neonates	38.0 ± 2.5	37.7 ± 2.9	38.0 ± 3.0	38.7 ± 2.0*

SEIFA Socio-Economic Indexes for Areas (0—lowest socio-economic area of residence, 10—highest socio-economic area of residence)

* $p < 0.01$, ** $p < 0.001$ (compared with the implant naltrexone group)

between rates of hospital admissions in naltrexone-treated women and either methadone- or buprenorphine-treated women during the three trimesters and the post-partum period. Similarly, there was no difference in rates of cause-specific admissions, with the exception of increased rates of hospital admissions with a mental health diagnosis in women treated with methadone (RR 1.68, 95% CI 1.25–2.28). Compared with the control group, rates of hospital admission were significantly elevated in the naltrexone cohort during the second trimester (RR 0.27, 95% CI 0.12–0.61) and the third trimester (RR 0.78, 95% CI 0.63–0.96). Rates of obstetric (RR 0.80, 95% CI 0.65–0.99) and mental health (RR 0.04, 95% CI 0.03–0.08) admissions were significantly higher in naltrexone-treated women than in control women.

Overall rates of ED attendance in the naltrexone-treated women were not significantly different to those in both methadone- and buprenorphine-treated women, as were rates during the three trimesters of pregnancy or post-partum. Overall rates of ED attendance in the naltrexone group were significantly higher than in the control group (RR 0.57, 95% CI 0.33–0.97), as were ED attendances during the second trimester (RR 0.35, 95% CI 0.18–0.66) and post-partum (RR 0.40, 95% CI 0.16–0.99). In addition, obstetric ED attendance and triage codes 3 (RR 0.37, 95% CI 0.19–0.73) and 5 (RR 0.35, 95% CI 0.17–0.73) were significantly higher in the naltrexone group than in the control group.

Three cases of opioid poisoning were observed in patients who attended hospital and/or the ED: one occurred in a naltrexone-treated women prior to treatment and the other two were in women treated with methadone (one while on methadone treatment, the other prior to treatment).

3.6 Pregnancy Complications: Reported at Birth

Rates of pregnancy complications reported at birth in naltrexone-treated mothers were not significantly difference to those in methadone- (odds ratio [OR] 1.01, 95% CI 0.58–1.76) or buprenorphine (OR 0.66, 95% CI 0.35–1.26)-treated mothers. There was no significant difference between naltrexone and methadone or buprenorphine in any of the cause-specific pregnancy complications. Compared with the naltrexone group, the control group had significantly lower rates of pregnancy complications (OR 0.50, 95% CI 0.27–0.91) and 'other' complications (OR 0.43, 95% CI 0.23–0.82) (Table 5).

3.7 Characteristics of Labour and Delivery

Lower rates of spontaneous labour/higher rates of induced labour were observed in buprenorphine-treated women than in the naltrexone-treated women. Similarly, rates of spontaneous vaginal birth were also significantly higher in naltrexone-treated women than in buprenorphine-treated women (Table 6). There was no significant difference between naltrexone-treated women and the other cohorts in their use of anaesthetics or analgesics, except for higher rates of the use of combined epidural/spinal anaesthetic in buprenorphine-treated women.

Rates of delivery complications in naltrexone-treated women were not dissimilar to those in methadone- and buprenorphine-treated women. Overall rates of labour complications in the naltrexone-treated women were not significantly different to the non-dependent controls (OR 0.54, 95% CI 0.29–1.03), although rates of fetal distress were significantly elevated in naltrexone-treated women

Table 5 Complications during pregnancy in opioid-dependent women treated with implant naltrexone ($n = 68$) compared with women treated with methadone ($n = 198$) or buprenorphine ($n = 126$) and controls ($n = 569$), as reported at birth in the Midwife Notification System

Complications	Naltrexone (%)	Methadone (%)	Buprenorphine (%)	Controls (%)
Any	55.9	58.1	47.6	35.3*
Threatened abortion <20 weeks[a]	0.0	2.0	3.2	4.2
Threatened pre-term labour <37 weeks	5.9	4.0	1.6	3.4
Urinary tract infection	1.5	6.6	6.4	3.7
Preeclampsia	1.5	4.6	2.4	3.2
Antepartum haemorrhage—placenta praevia	1.5	1.0	0.0	1.1
Antepartum haemorrhage—placenta abruption	1.5	0.5	0.8	0.5
Antepartum haemorrhage—other	2.9	7.1	2.4	4.2
Pre-labour rupture of membranes	8.8	9.1	4.8	3.7
Gestational diabetes mellitus	5.9	0.5	0.8	3.4
Other	35.3	38.9	36.5	16.5*

* $p < 0.05$ (compared with the implant naltrexone group)

[a] Vaginal bleeding with the uterus determined to be the source of bleeding before the 20th gestational week

Table 6 Labour and deliver characteristics in opioid-dependent women treated with implant naltrexone ($n = 68$) compared with those treated with methadone ($n = 198$) or buprenorphine ($n = 126$) and non-dependent controls ($n = 569$)

Labour and deliver characteristics	Naltrexone (%)	Methadone (%)	Buprenorphine (%)	Controls (%)
Onset of labour				
Spontaneous	49.5	44.4	38.9**	48.2
Induced	33.3	29.4	45.2*	30.2
No labour (caesarean)	17.2	16.2	15.9	21.6
Intended place of birth				
Hospital	100	100	100	96.7
Birth centre	0.0	0.0	0.0	3.3
Born before arrival	1.5	1.0	0.0	0.4
Delivery				
Spontaneous vaginal	63.2	57.6	53.2*	49.0
Assisted vaginal	16.2	18.2	17.5	17.1
Breech	1.5	0.5	1.6	0.0
Emergency caesarean	8.8	14.7	15.1	14.8
Anaesthetics and analgesics				
None	7.4	8.1	6.4	13.4
Epidural	51.5	46.0	56.4	53.6
Spinal block	11.8	9.1	5.6	14.6
Combined epidural/spinal block	8.8	18.2	21.4*	5.8
General	4.4	7.1	4.0	1.9
Nitrous oxide	38.2	40.9	41.2	28.1
Complication of labour or delivery				
Any	72.1	72.2	76.2	61.7
Precipitate delivery	7.4	9.1	0.8	4.6
Fetal distress	25.0	21.7	27.0	13.2**
Prolapsed cord[a]	0.0	0.5	0.8	0.0
Cord tight around neck	4.4	2.5	3.2	2.3
Cephalopelvic disproportion	0.0	0.5	0.0	2.1
Post-partum haemorrhage (≥500 mL)	17.7	23.2	23.8	8.4
Retained placenta—manual removal	4.4	1.0	3.2	1.6
Persistent occipito posterior	0.0	0.5	2.4	2.5
Shoulder dystocia	2.9	2.0	3.2	1.6
Failure to progress ≤3 cm	5.9	8.6	10.3	4.0
Failure to progress >3 cm[a]	0.0	3.5	3.2	4.9

* $p < 0.05$, ** $p < 0.01$ (compared with the implant naltrexone group)

compared with the control group (OR 0.29, 95% CI 0.14–0.61) (Table 7).

4 Discussion

4.1 Birth Rates

Birth rates in women treated with naltrexone were significantly elevated compared with all three comparison groups, with rates almost double that of women in the other three cohorts. The increased rate of birth in naltrexone-treated women may be attributable to the cessation of opioids (and restoration of menstruation) or a direct effect of naltrexone. Given the rates of pregnancy and previous pregnancy, contraception (including the use of long-term contraceptive options such as Implanon® [Merck Sharp & Dohme Corp., Whitehouse Station, NJ, USA]) should be an integral part of the drug and alcohol service for women, particularly those treated with implant naltrexone.

4.2 Maternal Mortality

No incidences of maternal death were noted in any of the four cohorts. This is not unexpected given the overall incidence of maternal mortality in Australia between 2006

Table 7 Rate of hospital admission and emergency department attendances per 100 pregnancies (reaching 20 weeks) during the three trimesters of pregnancy and the post-partum period in pregnant women treated with implant naltrexone, as compared with methadone or buprenorphine and a cohort of controls

Hospital admissions and ED attendances	Naltrexone	Methadone	Buprenorphine	Control
Hospital				
Admissions	179.4	187.4	157.0	135.0
Trimesters				
1	2.9	9.1	3.9	7.0
2	19.1	23.7	16.4	5.1**
3	152.9	146.0	128.1	119.3*
Post-partum	4.0	7.7	8.4	3.1
Admission with a diagnosis of				
Opioid poisoning	1.5	1.0	0.0	0.0
Non-opioid drug poisoning	0.0	1.5	0.8	0.0
Mental health	76.5	128.8**	84.4	3.7***
Obstetric	154.4	159.1	136.7	123.9*
Length of stay [days (IQR)]	4.3 (1–5)	4.6 (1–6)	4.8 (2–6)	3.8 (1–5)
ED[a]				
Attendances	124.5	183.1	178.4	55.8*
Trimesters				
1	32.1	33.1	41.6	17.0
2	57.4	63.7	62.9	24.0***
3	26.4	44.8	40.8	14.7
Post-partum	22.6	52.9	44.8	9.1*
Attendance with a diagnosis of:				
Opioid poisoning	0.0	0.6	0.0	0.0
Non-opioid drug poisoning	3.8	2.9	0.0	0.0
Mental health	1.9	4.1	2.4	0.4
Obstetric	18.9	18.0	12.8	5.0**
ED triage code[b]				
1	0.0	0.0	0.0	0.2
2	3.8	11.6	5.6	2.7
3	34.0	46.5	29.6	12.7**
4	35.8	46.5	44.8	22.2
5	50.9	92.4	98.4	18.1**

ED emergency department, *IQR* interquartile range

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ (compared with the implant naltrexone group)

[a] ED data only available from 2002 onwards; thus, only patients who conceived after 1 January 2002 were used in calculation of rates of ED attendance. Naltrexone, $n = 53$; methadone, $n = 172$; buprenorphine, $n = 125$; control, $n = 559$

[b] 1 = immediate (life-threatening), 2 = emergency (could become life-threatening), 3 = urgent (not life-threatening), 4 = semi-urgent, 5 = non-urgent (needs treatment when time permits)

and 2010 was 6.8 deaths per 100,000 women who gave birth (99 deaths nationally) [20].

4.3 Pregnancy Loss

Overall pregnancy losses prior to 20 weeks of gestation were significantly elevated in naltrexone-treated women compared with buprenorphine-treated women and controls (but not compared with methadone-treated women). Given that rates of birth in the naltrexone cohort were almost double that of the other three cohorts, it is not unexpected that rates of pregnancy loss would also be elevated. However, rates of ectopic pregnancies in naltrexone-treated women occurred at more than four times the rates of the three other treatment groups. Ectopic pregnancies are relatively common, occurring in approximately 1–2% of pregnancies in Europe and the USA [21]. In over 98% of ectopic pregnancies, the implantation occurs in the fallopian tube [21, 22]. Ectopic pregnancies are hypothesised to occur as the result of impaired embryo tubal transfer and/or alterations to the tubal environment allowing for early implantation to occur [22]. One pathway in which naltrexone may increase the rate of

ectopic pregnancies is via the regulation of nitric oxide (NO). Naltrexone has been shown to increase the activity of NO synthase (NOS) [23]. It is thought that NO, synthesized by inducible NOS, is involved in ciliary beat in the fallopian tubes, with increased levels relaxing the smooth muscle and potentially leading to higher rates of embryo retention [22]. In keeping with this, inducible NOS messenger RNA and protein levels have been shown to be greater in women with tubal ectopic pregnancies than in with pseudo-pregnant women [24].

4.4 Complications During Pregnancy, Labour and Delivery

Overall rates of complications during pregnancy (reported at birth) were elevated in naltrexone-treated women in comparison with the control groups; however, overall rates of hospital attendances and complications during labour were not significantly different. Notably, opioid-dependent women had high rates of hospital admissions with a mental health diagnosis compared with non-opioid-dependent women, which should be taken into account in the delivery of obstetric services to opioid-dependent women.

Naltrexone-treated women were generally not significantly different to those treated with both methadone and buprenorphine in terms of complications during pregnancy, labour and delivery. Rates of complications in the three opioid pharmacotherapy groups did not appear to be as high as reported by Dattel [25], who found an up to six-fold increase in prenatal obstetric complications in narcotic abusers.

The use of naltrexone in pregnancy was associated with high rates of spontaneous labour and spontaneous vaginal delivery compared with buprenorphine patients. While not significant, buprenorphine also appeared to have fewer incidences of precipitated delivery (7.4 vs. 0.8%), prelabour rupture of membranes (8.8 vs. 4.8%) and threatened pre-term labour (5.9 vs. 1.6%), and higher rates of failure to progress (5.9 vs. 13.5%). In contrast, delivery characteristics in methadone-treated women were very similar to naltrexone. The difference between buprenorphine and naltrexone or methadone in terms of delivery may be attributable to the agonist activity of buprenorphine on the orphan opioid receptor-like 1 (ORL-1), which is not acted on by either methadone or naltrexone. The ORL-1 and its endogenous ligand, prepronociceptin (PNOC) have been detected in the uterus of both pregnant and non-pregnant rats, with a moderate increase in PNOC with gestation [26]. PNOC was found to inhibit both potassium chloride (KCl)- and oxytocin-evoked rhythmic contractions, thus having a relaxing effect on the uterus. Interestingly, naloxone was found to significantly increase the effects of PNOC on the uterus; however, when used alone, the effect of naloxone was insignificant. As buprenorphine acts on the ORL-1, it could be assumed that it would also have a relaxing effect on the uterus, explaining the reduction in spontaneous labour, threatened pre-term labour and precipitate delivery, and the increased rates of failure to progress and induced labour. However, further research is required to support these findings.

The risk of opioid poisoning in pregnant women treated with naltrexone has been proposed as a potential problem [8]. Concerns regarding this have arisen from observations of increased rates of both fatal and non-fatal opioid poisoning following the cessation of oral naltrexone treatment in non-pregnant patients [15, 16]. These concerns led to the development of sustained-release naltrexone preparations, which slowly dose taper to prevent rapid changes in a patient's receptor occupancy and opioid tolerance. The move towards long-lasting naltrexone preparations has been shown to dramatically reduce opioid poisoning deaths in non-pregnant patients [15] and, as such, no opioid poisonings were observed in naltrexone-treated patients during pregnancy or in the post-partum period in this study.

Overall, naltrexone performed comparably to both methadone and buprenorphine, and thus patients who are stable on naltrexone treatment should be allowed to remain on treatment rather than being transferred onto an alternative agonist or partial agonist pharmacotherapy. However, further research is required to support these findings. For women who do become pregnant while on opioids or an opioid pharmacotherapy, support should be provided that takes into account the high rates of young, single women of a low socio-economic status, mental health disorders and HCV.

4.5 Strengths and Limitations

The rates of birth and complications reported in this study should be considered a minimum, with events occurring outside of WA not captured by the databases utilised. Additionally, ED data were not available prior to 2002; thus, pregnancy losses requiring ED attendance (but not hospital admission) would not have been captured. ED attendances are often not assigned a diagnosis, as it may be unclear.

Rates of pregnancy loss should also be considered to be only a portion of the actual rate, with the results not able to encapsulate planned medical abortions that occurred outside of hospital (e.g. in private clinics) or spontaneous abortions/miscarriages that did not result in the women attending a hospital or ED. In many cases, spontaneous abortions occur before a women realises she is pregnant. The absence of these results significantly underestimates the rates of conception.

It was assumed that patients who had been previously diagnosed with HCV still had the disease at the time of pregnancy and had not been treated. It is expected that treatment for HCV would have been minimal, given that HCV treatment is often restricted for patients who are at a high risk of becoming re-infected (i.e. via relapse to intravenous drug use). In WA, routine screening for HCV is generally carried out during the first trimester, and thus the capture of patients with HCV should be high.

Additionally, the study suffers from many of the limitations that occur in most epidemiological cohort studies, including a lack of randomisation. While the three groups appeared comparable in terms of the measured demographics, the three treatments may appeal to different patient groups in terms of their length of dependence (short- vs. long-term opioid users), motivation for treatment (maintenance vs. abstinence) or desired treatment outcome (drug-free life vs. risk management). Additionally, demographic information on a number of important variables was not available, including drug use history, concurrent drug use and use of contraception.

Comparisons between naltrexone-treated women and the control women should be interpreted with caution. The naltrexone group was significantly different to the control group in terms of a number of measured variables including smoking, socio-economic, HCV and marital status. Additionally the two groups are likely different in a number of other factors such as alcohol and other drug consumption, which would result in different maternal outcomes. For this reason, the difference between naltrexone-treated women and control women cannot be attributed solely to naltrexone. Moreover, the study only presents statistical comparisons between naltrexone-treated women and the three other groups. As such, it is unclear how maternal outcomes differ between the methadone and the control groups, the buprenorphine and control groups, and the methadone and buprenorphine groups. Similarly, no adjustments were made for multiple comparisons.

5 Conclusions

The use of implant naltrexone in opioid-dependent women was associated with a significant increase in birth rates, as compared with methadone, buprenorphine and controls. Overall rates of complications during pregnancy in naltrexone-treated women were elevated compared with control women, but were not significantly different to those seen in methadone- and buprenorphine-treated women.

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Compliance with Ethical Standards

Conflicts of interest Erin Kelty and Prof. Gary Hulse have no conflicts of interest to declare.

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