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Comparison of Pregnancy Complication Rates: Does Opioid Agonist Pharmacotherapy Make A Difference?

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Abstract

Background: Over the past decade, the prevalence of opioid use disorder (OUD) in pregnant patients has increased by 131% with an associated increase in pregnancy complications. Opioid agonist pharmacotherapy (OAP) with methadone or buprenorphine is recommended by ACOG for the management of OUD. The objectives of our study are to compare the incidence of pregnancy complications among patients who at the time of their delivery used OAP, OAP plus any additional substance (OAP+), illicit or prescribed opioids, and no opioids.

Methods: We conducted a retrospective cohort study at Berkshire Medical Center in Pittsfield, MA, between January 1, 2018, through December 31, 2020, to compare the incidence of nine pregnancy complications in patients who at the time of their delivery were using OAP, OAP+, illicit or prescribed opioids, and no opioids. The data was analyzed with Chi-squared tests and a Bonferroni correction of the p-value was used to adjust for comparison of the rates. The significance level used was $p \leq 0.025$.

Results: There were 1979 deliveries during the 3-year study period with a total complication incidence of 23%. The complication incidence was 11% for OAP, 15% for OAP+, 42% for illicit or prescribed opioids, and 24% for no opioids. The incidence of complications in the OAP group was significantly lower than the incidence in the no opioids group (11% vs 24%, $p = 0.01$). There was no significant difference in the comparisons between other groups.

Discussion: Our study investigated nine pregnancy complications; no other single study included all of these complications. Patients who used OAP had a significantly lower incidence of pregnancy complications compared to those who used no opioids. A multisite cohort study showed a low incidence of placental abruption in patients using methadone (3%), which was a similar outcome to the MOTHER study (2.3%) and our study (1.4%). The results of this research could assist providers in counseling their patients on the use of OAP in pregnancy.

Keywords

pregnancy complications, opioid agonist pharmacotherapy, methadone, buprenorphine, opioid use disorder

Conflict of Interest Statement

Alexa Pfeiffer, Pritha Aggarwal, and Michael Falcone are 3rd-year medical students from the University of New England College of Osteopathic Medicine (UNECOM) who were on clinical rotations at Berkshire Medical Center in Pittsfield, MA. Andrea Bodine, MD is an American College of Obstetrics and Gynecology certified physician, Associate Clinical Professor at UNECOM, and research mentor. We do not have any conflicts of interest or financial disclosures.

Cover Page Footnote

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ARTICLE

Comparison of Pregnancy Complication Rates: Does Opioid Agonist Pharmacotherapy Make a Difference?

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Abstract

Background: **Over the past decade, the prevalence of opioid use disorder (OUD) in pregnant patients has increased by 131% with an associated increase in pregnancy complications. Opioid agonist pharmacotherapy (OAP) with methadone or buprenorphine is recommended by ACOG for the management of OUD. The objectives of our study are to compare the incidence of pregnancy complications among patients who at the time of their delivery used OAP, OAP plus any additional substance (OAP+), illicit or prescribed opioids, and no opioids.**

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Discussion: **Our study investigated nine pregnancy complications; no other single study included all of these complications. Patients who used OAP had a significantly lower incidence of pregnancy complications compared to those who used no opioids. A multisite cohort study showed a low incidence of placental abruption in patients using methadone (3%), which was a similar outcome to the MOTHER study (2.3%) and our study (1.4%). The results of this research could assist providers in counseling their patients on the use of OAP in pregnancy.**

Keywords: Pregnancy complications, Opioid agonist pharmacotherapy, Methadone, Buprenorphine, Opioid use disorder

1. Introduction

The opioid crisis is a growing public health issue in the United States. Over the past decade, there has been a 131% increase in the number of pregnant patients with opioid use disorder (OUD) documented at the time of delivery, with an associated increase in pregnancy complications[1]. Opioid use in pregnancy can increase the patient's risk of cardiac arrest, placental abruption, preterm labor, oligohydramnios, blood transfusion, premature rupture of membranes, cesarean delivery, and death[2].

Opioid agonist pharmacotherapy (OAP) with methadone or buprenorphine is recommended by the American College of Obstetrics and Gynecology for the management of pregnant patients with OUD. The DSM-5 outlines 11 symptoms of OUD, two of which must be present to make the diagnosis. These symptoms include taking large amounts of opioids over a longer period than intended, and a persistent desire or unsuccessful efforts to cut down or control opioid use. Literature on OAP primarily highlights neonatal outcomes rather than pregnancy

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complications affecting the morbidity of the birthing person[3,4]. Neonatal complications have been well documented, especially for methadone use, including increased risk of preterm birth, small for gestational age, congenital anomalies, and neonatal abstinence syndrome (NAS)[5,6].Data broadly supports that the use of buprenorphine results in decreased NAS severity and risk of preterm birth[7,8]. There may be an increased risk of antenatal bleeding for pregnant patients who use OAP, including placental abruption and placenta previa, as shown by two Canadian studies[9,10].

Whether OAP use in pregnancy increases the risk of other obstetrical complications, such as gestational hypertension, pre-eclampsia, eclampsia, gestational diabetes mellitus, and postpartum hemorrhage remains to be clarified[11,12]. There is evidence that indicates pregnant patients prescribed methadone or buprenorphine have a greater incidence of delayed villous maturation, a larger placental size, and a decreased fetoplacental weight ratio compared to a control group[13]. Placental growth hormone is a contributing factor to insulin resistance and resultant gestational diabetes mellitus[14]. Hypertensive disorders and diabetes mellitus during pregnancy can affect the development of the placenta, which can lead to placental abruption[15]. The effects of OAP on the pathophysiology of these conditions outside of pregnancy have been reported in some animal studies. A study by Sadava et al. reveals a correlation between diabetes and methadone[16]. A physiologic explanation for this finding may be that beta-endorphins stimulate glucagon secretion in the absence of accompanying insulin secretion, which could contribute to hyperglycemia[17]. Both methadone and buprenorphine have been shown to be associated with improved nutrition and access to prenatal care, prevention of relapse, limitation of withdrawal symptoms, and reduction of infection compared to untreated OUD[18,19].

It is important to understand the risks and benefits of OAP during pregnancy to provide patients with data to make informed decisions. Our objectives were to compare the incidence of pregnancy complications among the four groups: patients who at the time of their delivery used OAP, OAP plus any additional substance (OAP+), illicit or prescribed opioids, and those who did not use any opioids (no opioids). Our primary hypothesis was that the incidence of pregnancy complications among patients who at the time of their delivery were using OAP compared to those who used no opioids would be similar. Our secondary hypothesis was that the incidence of pregnancy complications in patients who used OAP+ and those who used illicit or prescribed opioids would be increased compared to the other groups. The results of this research may help providers in counseling their patients who are considering starting or maintaining OAP during pregnancy, and update evidence-based best practices and guidelines.

2. Methods

We conducted a retrospective cohort study at Berkshire Medical Center (BMC) in Pittsfield, MA, to compare the incidence of nine pregnancy complications in patients who at the time of their delivery were using OAP, OAP+, illicit or prescribed opioids, and no opioids (Table 1). Our study looked at the records from all pregnant patients who delivered at BMC from January 1, 2018, through December 31, 2020. Inclusion criteria were all patients who delivered at BMC during the three-year study period. Exclusion criteria were pregnant patients who chose pregnancy termination options and those who were transferred to another hospital prior to delivery. IRB exemption was obtained.

Data was obtained from BMC Medical Records Department using ICD-10 codes to identify pregnant patients during the three-year study period who were using opioids at the time of delivery. The coding did not differentiate the types of opioids that were used. We reviewed the records of each patient to determine whether the patient was using OAP versus illicit or prescribed opioids. We documented any other substance use recorded at the time of

Table 1. Cohorts organized by opioid use status at the time of delivery

OAP	Methadone or buprenorphine
OAP+	OAP plus any additional illicit or recreational substance that may be detected on a urine toxicology screen such as amphetamines/methamphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, and opiates
Illicit or prescribed opioids	Morphine, hydromorphone, codeine, hydrocodone, oxycodone, fentanyl, carfentanil, meperidine, tramadol, and heroin; does not include patients who received opioids only as part of an epidural procedure
No opioids	No recorded opioid use and those who ceased use in the first trimester of pregnancy; patients who received opioids as part of an epidural procedure are included in this group

delivery, such as amphetamines/methamphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, and illicit opiates. The total number of deliveries by pregnant patients using OAP, OAP+, illicit or prescribed opioids, and no opioids was determined.

All patients with pregnancy complications over the study period were identified by BMC Medical Records Department using ICD-10 codes for placental abnormalities, hypertensive disorders, and other specified complications. Placental abnormalities were defined as placental abruption, placenta accreta, placenta percreta, and placenta increta. Hypertensive disorders were defined as gestational hypertension (GH), pre-eclampsia, and eclampsia. Other complications included gestational diabetes mellitus (GDM) and postpartum hemorrhage (PPH) (Table 2). We reviewed the records of all patients who had these pregnancy complications and documented those who at the time of delivery were using OAP, OAP+, illicit or prescribed opioids, and those who did not use any opioids (Fig. 1). The data was extracted from records and de-identified.

We calculated and compared the incidence of placental abnormalities, hypertensive disorders, and other complications at the time of delivery in each cohort. The data was analyzed with Chi-squared tests to determine if there was a significant difference in the incidence of pregnancy complications. A Chi-squared test is used for categorical data to determine whether there is a statistically significant difference between the expected results and the observed results. A Bonferroni correction of the p-value was used to adjust for the comparison of two rates against each other. The significance level used was $p \leq 0.025$.

3. Results

There were 1979 deliveries at BMC over the three-year study period. Of these, there were 72 deliveries with pregnant patients who used OAP only, 42 used OAP+, 12 used illicit or prescribed opioids, and 1854 used no opioids (Table 3). There were 460

Table 2. Pregnancy complication categories

Placental abnormalities	Placental abruption, placenta accreta, placenta percreta, placenta increta
Hypertensive disorders	Gestational hypertension (GH), pre-eclampsia, eclampsia
Other complications	Gestational diabetes mellitus (GDM), postpartum hemorrhage (PPH)

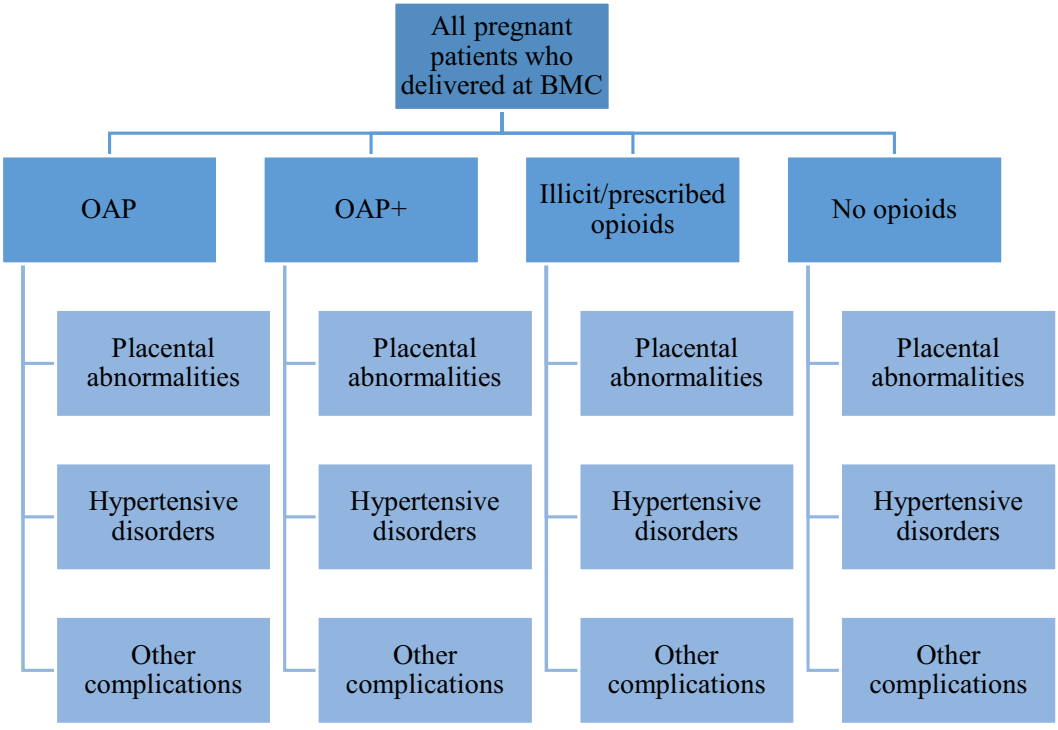

Fig. 1. Approach to data collection.

Table 3. Incidence of pregnancy complications in each cohort

Cohort	Deliveries	Pregnancy Complications	Incidence
OAP	72	8	0.11 (11%)
OAP+	41	6	0.15 (15%)
Illicit or Prescribed Opioids	12	5	0.42 (42%)
No Opioids	1854	441	0.24 (24%)
Total	1979	460	0.23 (23%)

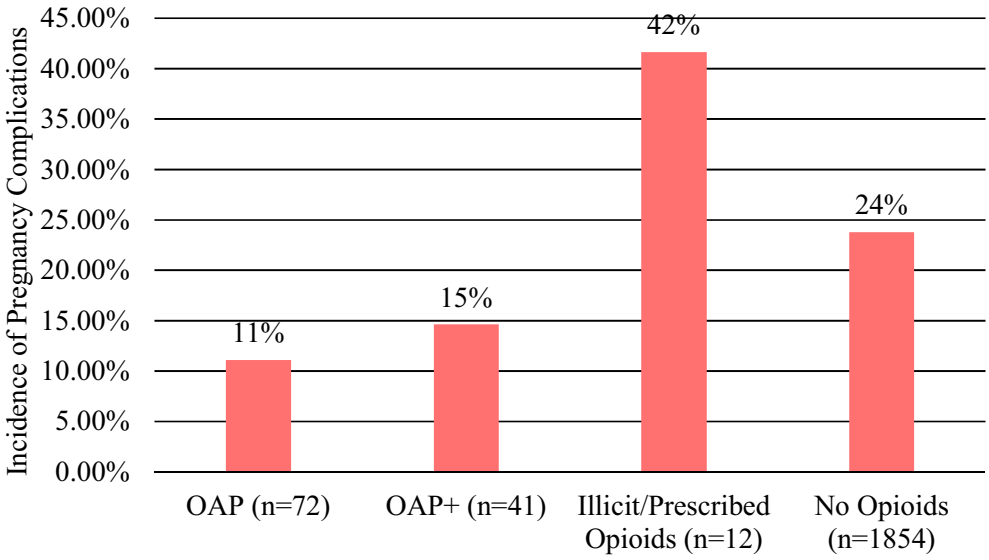

Fig. 2. Incidence of pregnancy complications in each cohort.

pregnancy complications that met the inclusion criteria, resulting in a total complication incidence of 23%. There were 8 complications for OAP only, 6 for OAP+, 5 for illicit or prescribed opioids, and 441 complications for no opioids (Table 3).

Of the total pregnancy complications, there were 16 placental abnormalities, 243 hypertensive disorders, and 201 other specified complications (Table 4). In the OAP group, there was 1 placental abnormality, 6 hypertensive disorders, and 1 other complication. In the OAP + group, there was 1 placental abnormality, 4 hypertensive disorders, and 1 other complication. In the illicit or prescribed opioids group, there were 2 placental abnormalities, 2 hypertensive disorders, and 1 other complication. In the no opioids group, there were 12 placental abnormalities, 231 hypertensive disorders, and 198 other complications (Table 4).

The total incidence of pregnancy complications over the three-year study period was 23% (n = 1979) (Table 3). For each individual cohort, the incidence was 11% for OAP (n = 72), 15% for OAP+ (n = 41), 42% for illicit or prescribed opioids (n = 12), and 24% for no opioids (n = 1854) (Table 3, Fig. 2).

The incidence of pregnancy complications in the OAP group was significantly lower than the incidence of pregnancy complications in the no opioids group (11% vs 24%, p = 0.01). There was no significant difference between OAP + vs. OAP (p = 0.58), illicit or prescribed opioids vs. OAP (p = 0.14), OAP + vs. illicit or prescribed opioids (p = 0.95), OAP + vs. no opioids (p = 0.17), and illicit or prescribed opioids vs. no opioids (p = 0.15) (Table 5).

4. Discussion

The incidence of pregnancy complications among patients who at the time of their delivery used OAP, OAP+, illicit or prescribed opioids, and no opioids was investigated in this study. A total of 1979 deliveries were included and divided into each cohort, and the incidence of pregnancy complications in each group was determined. The results demonstrated a significantly lower incidence of pregnancy complications in the OAP group compared to the no opioids group.

We primarily hypothesized that the incidence of pregnancy complications among patients who were using OAP compared to those who used no opioids would be similar. This hypothesis was rejected because we found a statistically significant

difference between these groups. Patients who used OAP had a lower incidence of pregnancy complications than patients who used no opioids (11% vs 24%, p = 0.01). This may be suggestive that OAP is not worse than taking no opioids during pregnancy. Reasons for this finding could include increased medication monitoring and more frequent prenatal visits because OUD in pregnancy classifies as high-risk. Our secondary hypothesis was that the incidence of pregnancy complications in patients who used OAP+ and those who used illicit or prescribed opioids would be increased compared to the other groups. The comparison of these incidence rates was not statistically significant. The small sample size of the cohorts led to underpowered results, from which we cannot draw any conclusions. This was most evident in the illicit or prescribed opioids cohort, which had the highest complication incidence (42%) and the smallest sample size where n = 12.

Our study investigated nine pregnancy complications related to gestational morbidity, which makes it unique because no one study included all of these complications. A multisite cohort study showed a low incidence of placental abruption in patients using methadone (3%), which was a similar outcome to the MOTHER study (2.3%) and our study (1.4%)[9]. In contrast, Miller et al. found that their OAP cohort had a higher rate of placental abruption (16%), compared to the 1% risk in the general population[10]. Guan et al. investigated complications in patients on methadone therapy; their research showed that 1.6% of patients who used OAP had severe maternal morbidity such as intrapartum hemorrhage, and 5.0% had other pregnancy complications including GDM, GH, and pre-eclampsia/eclampsia, which are lower rates than in our study[11]. A Canadian cohort study compared pregnancy complications in patients who used OAP, no opioids, and illicit opioids, with no significant difference in PPH between groups, which as in our study PPH accounted for less than 1% of complications in each group[12].

A strength of this research is that we accounted for illicit and recreational substances amongst those who use OAP, which reduced confounding bias from known pharmacological side effects. Potential confounders we did not account for include induction length, and opioid use prior to and during pregnancy. Due to the structure of this retrospective cohort study and the use of patient hospital records that were filtered by ICD-10 codes, there was inconsistent documentation of patients' history of opioid use, length of time of opioid use, and whether opioids were used throughout pregnancy, in early pregnancy, or prior to pregnancy. We were only able to determine the medications the patients were using at the time of delivery by viewing records from the labor and delivery unit. Many of the specified complications have well-known risk factors; morbidly adherent placenta is a strong risk factor for postpartum hemorrhage. While we had a

Table 4. Breakdown of pregnancy complication categories for each cohort

	OAP	OAP+	Illicit or Prescribed Opioids	No Opioids	Total Complications	
Placental Abruption	1	1	2	10	14	16 Placental Abnormalities
Placenta Accreta	0	0	0	2	2	
Placenta Percreta	0	0	0	0	0	
Placenta Increta	0	0	0	0	0	
GH	3	1	0	96	100	243 Hypertensive Disorders
Pre-Eclampsia	3	3	2	133	141	
Eclampsia	0	0	0	2	2	
GDM	0	0	1	139	140	201 Other Complications
PPH	1	1	0	59	61	
Total Complications	8	6	5	441	460	

Table 5. Statistical analysis comparing incidences in each cohort

Cohort Comparisons	Two-sided z-score	P-value (significance <0.025)
OAP vs. OAP+	0.55	0.58
OAP vs. Illicit/Prescribed Opioids	1.48	0.14
OAP vs. No Opioids	2.50	0.01[a]
OAP + vs. Illicit/Prescribed Opioids	0.06	0.95
OAP + vs. No Opioids	1.37	0.17
Illicit/Prescribed Opioids vs No Opioids	1.45	0.15

[a] denotes a significant comparison

large overall sample size, the distribution within each cohort was variable, which impacted the significance of the statistical analysis. The low sample size of the OAP+ and illicit/prescribed opioids groups resulted in underpowered comparisons.

Other limitations include the opportunity for error with inconsistent EMR documentation and retrieval of data. Our study population was selected from a single institution and geographic region, and we did not account for other health comorbidities, race, or socioeconomic status in our population. There were several patients who had multiple complications in the same pregnancy, and we accounted for each complication separately, which could inflate percentages. It is important to consider that our findings may be due to the transfer of high-risk patients with severe, known complications to a tertiary care center prior to delivery, however, due to the small number of patients seen by our community hospital, our sample size would have been further limited if we used more robust exclusion criteria. We did not review the time of initiation or the dose of OAP for each patient. We did not include nicotine as a substance of interest in our cohorts due to the inconsistency of reporting, and we did not separate people who used other illicit substances from the no opioids group.

Considerations for future research would be to repeat this study with a larger population such that we could make comparisons across multiple institutions and geographic regions. Comparing the OAP and illicit/prescribed opioids group would provide valuable clinical insight on the safety of these medications during pregnancy. It would also be important to separate people who use illicit substances identified on urine toxicology screening and nicotine from the no opioids group.

5. Conclusion

Pregnant patients who used OAP had a significantly lower incidence of pregnancy complications compared to those who used no opioids. The incidence of pregnancy complications in patients who used OAP + compared to illicit or prescribed opioids was not statistically significant. The results of this research show that there is a need for more studies that focus on pregnancy complications that affect the birthing person. If supported by further research across multiple institutions and geographical regions, the data found in this study could aid providers in counseling their pregnant patients on the relative safety of OAP initiation or maintenance.

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Author contribution

Conceptualization, Methodology, Supervision, Writing − original draft, Writing − review & editing

Conflict of interest

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