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Comparison of Postpartum Depression Incidence in Patients Undergoing Cesarean Section With and Without Ketamine Use: A Retrospective Cohort Study

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Abstract

Ketamine is increasingly being explored as a treatment for depression and has been studied for its potential prophylactic effects in postpartum depression (PPD). This study aims to analyze data from a large population to determine ketamine's efficacy in preventing PPD in patients without a prior history of depression and mitigating symptom escalation in those with a history of depression. Using data from TriNetX, a global health research network, we compare the incidence of PPD among patients who received ketamine during cesarean section delivery versus those who did not.

Background: Ketamine has gained attention as a potential treatment for depression, including postpartum depression (PPD). However, its role in preventing PPD remains uncertain, with conflicting findings in existing literature.

Objective: This study aimed to evaluate the association between ketamine use during cesarean section and the subsequent risk of PPD.

Methods: Data were extracted from TriNetX, a global health research network, to assess the incidence of PPD in patients who received ketamine during cesarean section versus those who did not. Risk analysis was conducted to determine the relative risk, odds ratio, and absolute risk difference.

Results: The incidence of PPD was significantly higher in the ketamine group (8.0%) compared to the non-ketamine group (2.6%), with a risk difference of 5.3% ($p = 0.000$). The risk ratio (3.017) and odds ratio (3.191) indicated that women who received ketamine were approximately three times more likely to develop PPD than those who did not.

Conclusion: These findings challenge the notion that ketamine provides a protective effect against PPD. Instead, they suggest that ketamine use during cesarean section may increase the risk of developing PPD, particularly in the absence of prior depression. Further research is needed to explore the underlying mechanisms and potential modifiers of this association.

Keywords: Ketamine; Postpartum Depression; Cesarean Section; Antidepressant

Abbreviations

PPD: Postpartum Depression; **EPDS**: Edinburgh Postnatal Depression Scale; **CS**: Cesarean section

Introduction

Postpartum depression (PPD) is a major depressive disorder occurring during pregnancy or

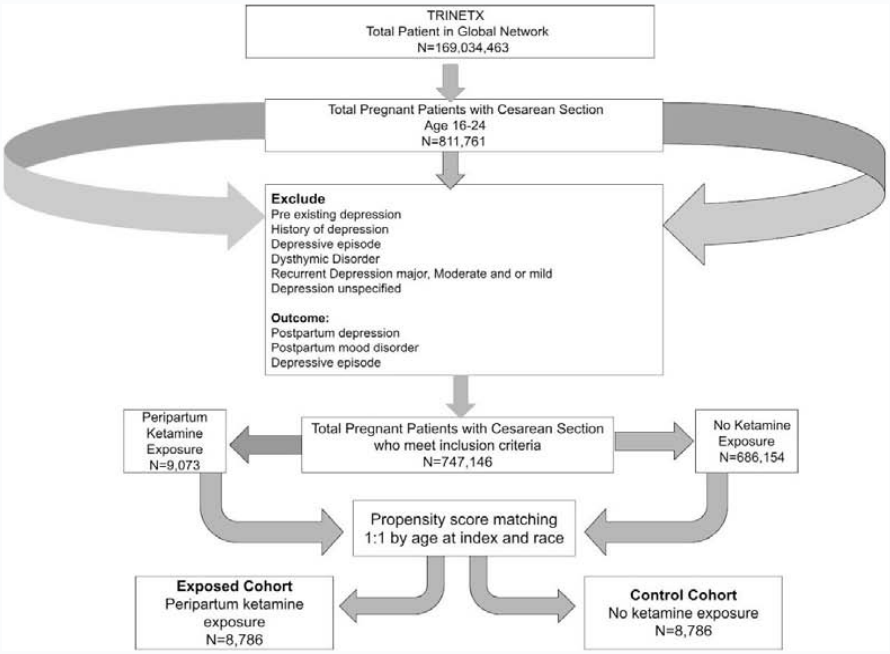


Figure 1: The exclusion criteria of the study and stratification of the patient population.

within four weeks postpartum, affecting approximately 1 in 7 women in the first year after childbirth. Symptoms include persistent sadness, sleep disturbances, difficulty bonding with the infant, and suicidal ideation [1]. PPD is influenced by a combination of psychosocial stressors, genetic predisposition, and hormonal fluctuations, particularly the sharp decline in estrogen and progesterone [2]. Diagnosis typically involves the Edinburgh Postnatal Depression Scale (EPDS). Known risk factors include a history of depression, family history of psychiatric disorders, high-risk pregnancy, lack of social support, and complications during delivery[3]. Conventional treatments involve therapy and medication, but recent research has sparked interest in ketamine as a potential treatment alternative due to its rapid-acting antidepressant effects [4].

Ketamine, which is commonly used as both an anesthetic and analgesic, has shown promise as a potential treatment for PPD. It is an N-methyl-D-aspartate (NMDA) receptor antagonist that induces dissociative anesthesia while maintaining cardiopulmonary stability, an advantage over traditional anesthetics. At subanesthetic doses, ketamine has also been found to possess antidepressant and analgesic properties, leading to benefits such as mood elevation, reduction in depressive symptoms, and anxiety relief [5]. Previous studies have suggested ketamine may reduce depressive symptoms in the postpartum period, but findings remain inconsistent [6].

Exploring ketamine for PPD prevention is particularly intriguing, given the limitations of conventional treatments. Although antidepressants have shown some efficacy in open trials for PPD, their results in controlled trials have been inconsistent. Ketamine's ability to address both labor pain and depressive symptoms, alongside its fast-acting antidepressant effects, suggests it may play a preventive role in PPD development. Its combined analgesic, anesthetic, and antidepressant actions may also contribute to more positive postpartum outcomes [4].

The need for effective treatments and preventative measures for PPD is critical. This condition not only causes significant morbidity in mothers but also affects the well-being of their children. This investigation seeks to critically evaluate the existing research on ketamine's potential in reducing the prevalence of PPD and its possible application in obstetric care.

Methods

This study employed a retrospective cohort design to investigate the incidence of postpartum depression in pregnant patients who received ketamine for caesarean section compared to those who did not receive such treatment. De- identified electronic medical records from the TriNetX database analyzed patient data from January 1st, 2004 to December 31st, 2024. TriNetX is a global health research network which analyzes electronic health data, including laboratory values, diagnoses, procedures, and medications. This data is reflective of electronic medical records sourced from 93 healthcare organizations (HCOs) which form a collective network. This data acquisition process utilizes Natural Language Processing (NLP), a form of artificial intelligence, to process data from human language.

TriNetX yielded an initial study population of 811,761pregnant women who received cesarean sections (Figure 1). This number was then purged to 747,146 after adjusting for exclusion criteria. The exclusion criteria in this investigation included women with a prior history of depressive episodes or a previous diagnosis of unspecified depression, dysthymic disorder, or major depressive disorder prior to their cesarean section. The remaining study population was then categorized into two cohorts, exposed and controlled, based on their exposure to ketamine. Those who received ketamine during their routine caesarean section were assigned into the exposed cohort. Those without exposure to ketamine were grouped into the control cohort.

After accounting for ketamine exposure, the study population was stratified into a final exposed cohort of 9,073 patients and a control cohort of 686,154 patients (Table 1). Using 1:1 propensity score matching (PSM), the study cohorts were matched for demographic

Table 1: The characteristics of the two cohorts before and after propensity score matching with the exposed and control cohorts represented as cohort 1 and 2 respectively.

Cohort 1 (N = 601,413) and cohort 2 (N = 8,601) characteristics before propensity score matching							
Demographics							
Cohort			Mean ± SD	Patients	% of Cohort	P-Value	Std diff.
1	AI	Age at Index	30.4 +/- 6.7	582,695	100%	<0.001	0.167
2			29.4 +/- 6.3	8,597	100%		
1	2106-3	White		231,664	39.8%	<0.001	0.229
2				4,391	51.1%		
1	1002-5	American Indian or Alaska Native		997	0.2%	<0.001	0.037
2				31	0.4%		
1	UNK	Unknown Race		240,341	41.2%	<0.001	0.739
2				930	10.8%		
1	2076-8	Native Hawaiian or Other Pacific Islander		1,917	0.3%	<0.001	0.061
2				67	0.8%		
1	2054-5	Black or African American		49,431	8.5%	<0.001	0.461
2				2,176	25.3%		
1	2131-1	Other Race		26,539	4.6%	<0.001	0.106
2				604	7.0%		
1	2028-9	Asian		31,806	5.5%	<0.001	0.038
2				398	4.6%		

characteristics, resulting in 8,786 patients in each cohort (Table 1). The effect of ketamine administration on postpartum outcomes over one month, six months, and one year was then assessed through risk analysis, Kaplan-Meier survival analysis, and hazard ratio calculations. The incidence of postpartum depression (PPD) and general depression served as the primary outcomes for these evaluations.

Results

The study findings indicate that ketamine administration during cesarean section (CS) was associated with a significantly higher risk of both postpartum depression and general depression over a one-year follow-up period.

Within the first month postpartum, postpartum depression was diagnosed in 0.637% of patients in the control group (CS without ketamine) compared to 1.616% in the ketamine group (CS with ketamine), with a statistically significant risk difference of 0.979% (95% CI: 1.291% to 0.667%, $p < 0.0001$). Similarly, depression was more prevalent in the ketamine group (2.857%) compared to the control group (1.502%), with a risk difference of 1.354% (95% CI: 1.786% to 0.923%, $p < 0.0001$) (Table 2). Kaplan-Meier survival analysis confirmed that the probability of remaining free from postpartum depression and depression was significantly lower in the ketamine group compared to the control group (Table 3).

At six months postpartum, the trend persisted, with postpartum depression affecting 1.559% of patients in the control group and 3.49% in the ketamine group (risk difference: -1.931%, 95% CI: -2.399% to -1.463%, $p < 0.0001$). Similarly, the incidence of general depression was higher in the ketamine group (4.42%) than in the control group (2.07%), with a risk difference of -2.35% (95% CI: -2.878% to -1.821%, $p < 0.0001$) (Table 4). Kaplan-Meier survival analysis and hazard ratios further demonstrated the significantly higher risk of depression in the ketamine group (Table 5).

By the one-year follow-up, postpartum depression was diagnosed in 1.389% of the control group and 3.71% of the ketamine group (risk difference: -2.322%, 95% CI: -2.787% to -1.857%, $p < 0.0001$). General depression also remained significantly more prevalent in the ketamine group (4.928%) compared to the control group (2.31%), with a risk difference of -2.618% (95% CI: -3.169% to -2.067%, $p < 0.0001$) (Table 6). The survival analysis consistently showed a lower probability of remaining depression-free in the ketamine group, and statistical tests confirmed a significantly higher hazard ratio for depression in this group across all follow-up periods (Table 7).

Discussion

Our study sought to evaluate whether ketamine administered during cesarean sections had a protective effect against postpartum depression (PPD). Contrary to our initial hypothesis, the results indicate that ketamine use during C-sections is associated with a significantly higher incidence of PPD compared to women who did not receive ketamine. The survival analysis further supports this, showing a lower probability of remaining free from PPD in the ketamine group, and the hazard ratio confirms an increased risk of developing depression over time in these patients.

The risk analysis revealed that the incidence of PPD was markedly higher in the ketamine group (8.0%) compared to the non-ketamine group (2.6%). The difference in risk (5.3%) was highly statistically significant, with a p-value of 0.000. Both the risk ratio (3.017) and odds ratio (3.191) indicate that women who received ketamine were approximately three times more likely to develop PPD than those who did not. These findings contradict previous studies that suggested a protective effect of ketamine against PPD, instead highlighting a strong association between ketamine use and an increased risk of PPD in this cohort.

Table 2: Risk of Postpartum Depression in cesarean section patients with and without peripartum ketamine exposure at one month follow up.

Cohort 1 (N = 8,597) and cohort 2 (N = 8,597) characteristics after propensity score matching							
Demographics							
Cohort			Mean ± SD	Patients	% of Cohort	P-Value	Std diff.
1	AI	Age at Index	29.4 +/- 6.3	8,597	100%	0.983	<0.001
2			29.4 +/- 6.3	8,597	100%		
1	2106-3	White		4,391	51.1%	1	<0.001
2				4,391	51.1%		
1	1002-5	American Indian or Alaska Native		30	0.3%	0.898	0.002
2				31	0.4%		
1	UNK	Unknown Race		930	10.8%	1	<0.001
2				930	10.8%		
1	2076-8	Native Hawaiian or Other Pacific Islander		67	0.8%	1	<0.001
2				67	0.8%		
1	2054-5	Black or African American		2,176	25.3%	1	<0.001
2				2,176	25.3%		
1	2131-1	Other Race		605	7.0%	0.976	<0.001
2				604	7.0%		
1	2028-9	Asian		398	4.6%	1	<0.001
2				398	4.6%		

Table 3: An assessment of the survival probability of not developing PPD and the hazard ratio of developing PPD between the two cohorts over the one month follow up period.

1 postpartum depression Risk Analysis in cohort patients with outcome				
Risk analysis				
Cohort	Patients in cohort	Patients with outcome	Risk	
Control	8,786	56	0.006	
Ketamine new	8,786	142	0.016	
		95% CI	z	p
Risk Difference	-0.010	(-0.013, -0.007)	-6.146	0.000
Risk Ratio	0.394	(0.290, 0.537)	N/A	N/A
Odds Ratio	0.390	(0.286, 0.533)	N/A	N/A

Several studies have previously evaluated the potential of ketamine to reduce postpartum depressive symptoms. For example, a double-blind, randomized clinical trial conducted in 2020 investigated the use of intraoperative ketamine in Chinese women undergoing C-sections. In this study, women were administered a low dose of ketamine (0.25 mg/kg) within five minutes of cord clamping. The Edinburgh Postnatal Depression Scale (EPDS) was used to assess depressive symptoms at one week, two weeks, and one month postpartum. Interestingly, the study found a significant reduction in EPDS scores at one week postpartum in the ketamine group compared to placebo, but this effect was not sustained at two weeks or one month. Additionally, women in the ketamine group reported lower pain scores two days postpartum, but experienced higher rates of short-term side effects such as headaches, hallucinations, and dizziness [7]. These findings suggest that while low-dose ketamine may provide short-term benefits in reducing depressive symptoms, the long-term effects are unclear, and higher doses such as those used in our study (which are approximately 10 times higher) may not offer similar protection.

Another randomized controlled study from 2019 investigated the prophylactic use of ketamine at a dose of 0.5 mg/kg administered 10 minutes after cesarean delivery. This study found that ketamine administration reduced postpartum depressive symptoms and protected against risk factors such as antenatal depression and stress [8]. Similar to the 2020 study, ketamine was associated with decreased postoperative pain and reduced opioid need. However, the dose used in this trial was significantly lower than the dose typically used during cesarean sections for anesthesia. These lower doses may explain the observed protective effect, as higher doses could lead to different physiological responses, especially in the context of the postpartum period.

Our study, which utilized a higher dose of ketamine typical for anesthetic purposes during C-sections, reveals a different outcome. The hazard ratio of 2.874 in our cohort indicates that women who received higher doses of ketamine had nearly three times the risk of developing PPD compared to the non-ketamine group. While previous studies have shown some short-term benefits of ketamine in reducing depressive symptoms [1], particularly at lower doses, our findings suggest that higher doses administered during surgery may not confer the same protective effect and may instead elevate the risk of PPD.

There are several possible explanations for these divergent findings. First, the physiological context of the postpartum period—including hormonal changes, sleep deprivation, and surgical recovery—could alter the way ketamine interacts with the brain. This unique physiological state may reduce the efficacy of ketamine or even contribute to the development of depressive symptoms [9,10]. Furthermore, while ketamine has shown rapid antidepressant effects in other settings[1], its long-term efficacy is less clear, particularly in postpartum women. The data from our study suggest that the short-term antidepressant effects observed in earlier trials [3] may not

Table 4: The risk difference, risk ratio, and odds ratio comparison of the exposed and non-exposed cohorts at 6 month.

Kaplan - Meier survival analysis in cohort patients with outcome					
Cohort	**Patients in cohort**	**Patients with outcome**	**Median survival (days)**	**Survival probability at end of time window**	
Control	8,786	56	--	99.26%	
Ketamine new	8,786	142	--	98.21%	
	χ^2	**df**	**p**		
Log-Rank Test	33.275	1	0		
	Hazard Ratio	**95% CI**	**χ^2**	**df**	**p**
Hazard Ratio and Proportionality	0.414	(0.304, 0.564)	0.182	1	0.670

Table 5: An assessment of the survival probability of not developing PPD and the hazard ratio of developing PPD between the two cohorts over the one month follow up period.

1 postpartum depression				
Risk analysis				
Cohort	**Patients in cohort**	**Patients with outcome**	**Risk**	
Control	8,597	134	0.016	
Ketamine new	8,597	300	0.035	
		95% CI	**z**	**p**
Risk Difference	-0.019	(-0.024, -0.015)	-8.071	0.000
Risk Ratio	0.447	(0.365, 0.546)	N/A	N/A
Odds Ratio	0.438	(0.356, 0.538)	N/A	N/A

Table 6: The risk difference, risk ratio, and odds ratio comparison of the exposed and non-exposed cohorts at 1 year.

Kaplan - Meier survival analysis in cohort patients with outcome						
Cohort		**Patients in cohort**	**Patients with outcome**	**Median survival (days)**	**Survival probability at end of time window**	
1	Control	8,786	112	--	98.42%	
2	Ketamine new	8,786	304	--	95.92%	
		χ^2	**df**	**p**		
Log-Rank Test		80.573	1	0.000		
		Hazard Ratio	**95% CI**	**χ^2**	**df**	**p**
Hazard Ratio and Proportionality		0.385	(0.310, 0.478)	0.237	1	0.626

Table 7: An assessment of the survival probability of not developing PPD and the hazard ratio of developing PPD between the two cohorts over one year follow up period.

1 postpartum depression					
Risk analysis					
Cohort		**Patients in cohort**	**Patients with outcome**	**Risk**	
1	Control	8,786	122	0.014	
2	Ketamine new	8,786	326	0.037	
			95% CI	**z**	**p**
Risk Difference		-0.023	(-0.028, -0.019)	-9.763	0.000
Risk Ratio		0.374	(0.305, 0.460)	N/A	N/A
Odds Ratio		0.365	(0.296, 0.451)	N/A	N/A

translate into long-term prevention of PPD, especially when higher doses are used.

Additionally,the dose administered during C-sections is approximately ten times higher than the doses used in prior studies evaluating its antidepressant effects. Such high doses could lead to adverse neurochemical and cardiovascular effects, including exacerbation of preeclampsia or increased catecholamine levels, particularly in high-risk patients [9, 10]. Ketamine's pharmacological properties may also play a role in the increased incidence of PPD observed in our study. Ketamine's ability to cross the placenta, due to its lipophilic properties, brings up issues regarding dosing and teratogenicity [12]. These side effects could contribute to the increased risk of PPD observed in our study.

Future Directions

It is difficult to define the ideal indications for the use of ketamine in the obstetric context due to multiple intervening variables. The majority of the previous research that highlights the benefits of ketamine as an antidepressant, analgesic, and anesthetic has studied its impacts in medical and surgical environments devoid of caring for both mother and baby [13]. Ketamine is a highly lipophilic anesthetic and, therefore, has the potential to cross the placenta. Its lipophilic nature incurs concerns about dosing and the possibility of teratogenicity [12]. To avoid harm to the mother and fetus, most peripartum doses are maintained at less than 1.5 mg/kg. Previous studies have found positive analgesic effects at subdissociative doses of <0.3 mg/kg [13]. Therefore, framing an optimal dose for obstetrics would require further study investigating the delicate balance between optimizing effectivity without introducing teratogenicity.

Obstetrics is a setting that uniquely cares for both mother and baby. Some obstetric complications and pathologies have competing physiologies that would be inversely affected by medical interventions. As well, pregnancy is characterized by physiological changes that would denote the need for further study into the interactions between peripartum alterations and the physiological effects of ketamine [12]. For instance, pre-eclampsia can only be resolved by the birth of the fetus. However, ketamine preserves systemic vascular resistance, which would cause the persistence of the perfusion aberration associated with pre-eclampsia. Furthermore, ketamine promotes an increase in catecholamines and should be avoided in high-risk patients [13].

Postpartum depression is a long-term sequel to the peripartum state in which ketamine is administered. The proposed value of ketamine in blunting the prevalence of PPD is linked to its effects on reducing dysthymia and alleviating labor pains. Previous studies have proven that ketamine is successful in producing both of those outcomes [13]. However, these positive effects were measured during follow-up periods of less than three weeks. Moreover, case reports have also established a precedence of ketamine protecting against PPD in individuals with a history of depression [12]. This observation was also measured soon after the individual was discharged after childbirth. These findings underscore the lack of insight into the long-term value of ketamine in reducing the risk of developing PPD; a diagnosis that is made 4 to 6 weeks after childbirth. Continually, there is very little research investigating the risks and benefits of long-term ketamine use while breastfeeding [13].

Previous literature has established ketamine as an informed alternative approach to mitigating the incidence of PPD. This is evidenced by its proven value as an analgesic and antidepressant with added benefits of sedation and cardiopulmonary preservation [12]. However, most of its valuable benefits have only been observed over an acute timeline, such as 10 minutes post-cesarean section or 1 week after discharge. To evaluate its efficacy in preventing the development of PPD, further research studies would have to measure PPD metrics at least 6 weeks after the initial administration or investigate the effectiveness of long-term ketamine regimens post-childbirth. Moreover, framing the optimal considerations for the standardized obstetric use of ketamine would require multifactorial approaches investigating follow-up timelines, pre-existing depression, dosage series, and evaluating multiple ranges of subanesthetic doses [13].

Limitations

Despite the significant findings of this study, several limitations should be considered. First, the study is observational in nature, which limits the ability to establish a direct causal relationship between ketamine administration and increased risk of postpartum depression. Other confounding factors, such as pre-existing mental health conditions, genetic predisposition, or social and environmental influences, may have contributed to the observed outcomes.

Second, the study did not account for variations in ketamine dosage, duration of administration, or potential interactions with other anesthetic agents, which could have influenced the results. Additionally, factors such as pain management protocols, psychological support, and postpartum care were not controlled for, potentially affecting the incidence of postpartum depression in both groups.

Third, while the follow-up periods extended to one year postpartum, longer-term effects of ketamine exposure during cesarean delivery remain unknown. Future research with extended follow-up durations could provide further insight into the long-term mental health implications of ketamine use during childbirth.

Lastly, the study population may not be fully representative of all women undergoing cesarean sections, as differences in demographics, healthcare systems, and individual medical histories may impact the generalizability of the findings. Further research, including randomized controlled trials and multi-center studies, is needed to confirm these results and better understand the potential risks associated with ketamine use in obstetric anesthesia.

Conclusion

Postpartum depression is a serious condition that affects mothers, their children, and families. This study found that ketamine administration during cesarean section was associated with a significantly higher incidence of postpartum depression compared to those who did not receive ketamine. These findings challenge the notion of a protective effect and underscore the need for careful anesthetic selection in childbirth. Further research is needed to understand the mechanisms behind this association and to develop strategies for reducing postpartum depression risk in women undergoing cesarean sections.

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