Safe Ketamine Use and Pregnancy:

A Nationwide Survey and Retrospective Review of Informed Consent, Counseling, and Testing Practices

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Abstract

Objective: Ketamine is contraindicated in pregnancy given the lack of knowledge about potential effects on a developing fetus. This study aimed to characterize current clinical practices specific to pregnancy and reproduction related to the use of ketamine for the treatment of psychiatric illness.

Methods: Online surveys were sent to outpatient ketamine clinics across the United States inquiring about practices related to pregnancy. Responses were collected between September and November 2023. Additionally, a retrospective medical record review was conducted to ascertain the frequency of pregnancy testing and contraception use with ketamine treatments administered at a large academic health system. Online, publicly available informed consent documents were also reviewed for language related to pregnancy.

Results: Fewer than half of survey respondents (n = 126) discuss specific risks related to pregnancy and fetal ketamine exposure during the informed consent process. Twenty percent of clinics require pregnancy tests prior to treatment, and 10.5% require subsequent testing during treatment; however, 22.9% of clinics do not have a standard process for testing. Only 13.7% of clinics specifically recommend or require use of contraception. Retrospective record review revealed that all patients who received intravenous ketamine for psychiatric indications in an academic medical center were pregnancy tested weekly, but only half were using contraception during treatment.

Conclusion: Many women with the potential to become pregnant are treated with ketamine for psychiatric illness. Results of the present study reveal that risks of fetal ketamine exposure are often overlooked, indicating a need for increased awareness about reproductive concerns when prescribing ketamine for the treatment of psychiatric disorders.

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The use of ketamine, an *N*-methyl-D-aspartate (NMDA) receptor antagonist and dissociative anesthetic, is becoming increasingly common in the practice of psychiatry. It has demonstrated efficacy in rapidly and substantially reducing depressive symptoms and suicidal ideation in patients with treatment-resistant depression (TRD) and has shown promising preliminary results for other psychiatric conditions.[1–3] Specific evidence-based practice guidelines are limited,[4] and ketamine treatment courses can vary widely in duration, frequency, schedule, dosing, and route of administration.[5,6] Intranasal esketamine, the *S*-enantiomer of racemic ketamine (marketed as Spravato), is the only formulation approved for use by the Food and Drug Administration (FDA) for TRD, and, as such, its use is more standardized and regulated, but treatment courses are still subject to variability. The use of maintenance ketamine, including intranasal esketamine and sublingual racemic ketamine, for ongoing treatment of depression is also becoming more common as long-term efficacy and safety studies demonstrate positive findings.[7] Given at subanesthetic doses for psychiatric indications, ketamine is generally considered safe and is typically well tolerated; however, there are still significant gaps in knowledge about ketamine use in special patient populations.[8] The FDA has clearly indicated that ketamine is not recommended in pregnancy as little is known about its effect on a developing fetus. Prescribing information for intranasal esketamine also includes a statement that patients should be specifically informed of the potential risk for fetal harm secondary to in utero ketamine exposure and should be advised about pregnancy prevention while receiving this treatment.[9] Despite this, there is minimal information available to guide prescribers about how to effectively counsel patients and manage concerns about pregnancy during a course of ketamine treatment for psychiatric illness.[10]

Editor's Note
We encourage authors to submit papers for consideration as a part of our Focus on Women's Mental Health section. Please contact Marlene P. Freeman, MD, at mfreeman@psychiatrist.com.

Clinical Points

- Outpatient ketamine prescribing for psychiatric illness is increasingly common; however, there is little information about how this care is being delivered in the community.
- There are some guidelines available to inform clinical practice, but pregnancy and reproductive concerns are infrequently considered.
- Ketamine treatment for psychiatric illness should be avoided in pregnancy due to the potential risk for teratogenicity.
- There is variability in practice among outpatient ketamine clinics in the community; however, pregnancy testing, informed consent, and reproductive counseling practices specifically are often insufficient.
- Prior to starting ketamine treatment, pregnancy testing should be strongly recommended for all patients with the potential to become pregnant and should be repeated throughout the treatment course.
- The informed consent process should include a discussion of reproductive risks, and the need for ongoing pregnancy prevention should be emphasized, especially in cases involving long-term maintenance treatment.

Ketamine readily and rapidly crosses the human blood-placental barrier and preferentially distributes to neuronal tissue in preclinical models.[11,12] Racemic ketamine and esketamine have elimination half-lives of 2–4 hours and 7–12 hours, respectively. While there are no studies directly examining the effects of perinatal ketamine exposure in humans, there is potential for the disruption of normal embryogenesis, especially in the early stages of development when these critical processes are most vulnerable.[13] Animal studies have associated ketamine exposure with significant neurotoxic effects including, but not limited to, neuronal cell death, changes in NMDA receptor expression patterns, aberrancies in synaptogenesis, and abnormal neural pathway development.[13,14] Offspring exposed to ketamine during the prenatal period have demonstrated lasting behavioral, cognitive, and affective disturbances including an enduring symptom pattern that has been used as an animal model of schizophrenia.[15,16] Of more direct relevance to humans, studies conducted in nonhuman primates have shown that ketamine use during pregnancy causes neurodegeneration apoptosis in the fetal brain in addition to significant and long-lasting cognitive deficits if used during the first weeks of life.[17,18] A reported case of a neonate with confirmed exposure to ketamine in utero demonstrated several abnormalities including marked hypotonia, hyporeflexia, and evidence of "moderate cerebral dysfunction" on electroencephalogram.[19] In utero exposure to phencyclidine, an NMDA receptor antagonist and close analog of ketamine, has also been associated with neonatal withdrawal syndrome in addition to neurological and behavioral abnormalities in exposed infants.[20–22] While these findings do not prove neurotoxicity in human development, they are cause for significant concern in the context of potential fetal exposure. This is especially pertinent to ketamine use for psychiatric indications as exposure has the potential to be early in development and repetitive throughout the treatment course. Nearly 10% of women of childbearing age become pregnant in a 12-month period, and almost half of these pregnancies are unplanned.[23] Therefore, reproductive potential should be taken into consideration during a course of ketamine treatment, especially in cases involving long-term maintenance.

Patients with the potential to become pregnant during treatment have a right to be informed about ketamine's possible teratogenic effects and should be counseled appropriately prior to the initiation of a treatment course. The American Society of Ketamine Physicians, Psychotherapists, and Providers (ASKP3) has published "Standards of Practice in the Therapeutic Use of Subanesthetic Ketamine" which provides guidance for safe and effective prescribing, however, does not include language about pregnancy or reproductive concerns.[24] Spravato prescribing information includes a statement that patients should be specifically informed of the potential risk for fetal harm secondary to in utero ketamine exposure and should be advised about pregnancy prevention while receiving this treatment.[7] Although Spravato use is restricted through the Risk Evaluation and Mitigation Strategy program to prevent adverse outcomes related to dissociation and to ensure adequate monitoring, it does not specify pregnancy as a safety consideration.[9] A standard has been proposed recommending pregnancy testing prior to starting ketamine treatment and weekly for the duration of the treatment course; however, it is unknown how widely this practice has been adopted.[25] Likewise, there are no specific recommendations about how to counsel patients on the possible risks of fetal exposure during the informed consent process or to discuss the potential need for use of contraception during treatment.[26]

The aim of this study was to assess current pregnancy screening or testing practices, counseling strategies, and informed consent processes at outpatient ketamine clinics across the nation. A retrospective medical record review was also performed examining practices related to pregnancy within a large academic health system with a robust ketamine treatment program in the midwestern United States.

METHODS

All components of this study were approved by the University of Michigan Institutional Review Board.

Survey

We used Qualtrics software (Qualtrics, Provo, UT) as our online platform for survey design and distribution to conduct a 20-question, cross-sectional survey designed to obtain information about pregnancy and reproduction in the context of ketamine treatment for psychiatric illness. Clinic contact information was obtained through publicly available listings from 4 online ketamine clinic directories (ASKP3 Directory, Ketamine Directory, Ketamine Clinic Directory, and Find Ketamine Directory). All clinics with a listed email address were invited to participate in this survey. A general request for participation was sent via email to 484 ketamine clinics across the United States. Survey questions elicited a combination of general clinic information such as the practice's geographic location, clinic volume, and patient demographics, in addition to specific practices related to pregnancy including the clinic's pregnancy testing policies, informed consent processes, and recommendations for contraception use. Question styles included forced choice, select all, and open-ended response. Nested questions were utilized to allow respondents to provide additional detail if relevant responses were selected. After completing the survey, respondents were given the option to share an email address to be included in a drawing for a $50 gift card for their participation. Responses were accepted from September through November 2023. At the conclusion of the survey, responses were aggregated, and percentage data were calculated. All survey responses were de-identified to protect participant anonymity.

Consent Document Search

Two search engines (Google and Bing) were queried to obtain publicly available informed consent documents from ketamine clinics nationwide. Search terms included "ketamine clinic informed consent" and "ketamine clinic informed consent document(s)." Search results were reviewed, and relevant web links were accessed. Informed consent documents were obtained and examined in detail for content related to pregnancy or reproductive considerations. Specific information extracted included the presence or absence of language about pregnancy in general, additional details about potential risks of fetal ketamine exposure, and any requirements or recommendations for pregnancy testing and/or contraception use during treatment.

Retrospective Medical Record Review

Electronic medical record search tools were used to identify a cohort of patients within a sample of over 3 million unique patients seen within a large academic health system in the midwestern United States. This cohort included all patients who received 1 or more doses of intravenous (IV) ketamine for a primary psychiatric indication that were biologically female and between the ages of 18 and 50 years at the time of treatment. Individual patient charts were accessed to review the details of their ketamine treatment course including schedule and frequency of pregnancy tests obtained and information about contraception use. This cohort included all patients who received at least 1 ketamine treatment within the institution prior to November 2023.

RESULTS

Survey

A total of 126 survey responses were recorded (26% response rate). Responses indicating that a clinic does not prescribe ketamine for at least 1 psychiatric indication were excluded from aggregated data (n = 119). Geographic distribution of respondents corresponded roughly to the population density of each region based on 2022 estimates from the United States Census Bureau with 16.1% of respondents from the Northeast, 22.6% from the Midwest, 35.5% from the South, and 25.8% from the West.[27] Respondents estimate cumulatively treating 7,480 individual patients in a 30-day period and report that approximately 33.7% of these patients are premenopausal biological females. Ketamine was most commonly prescribed for the indication of treatment-resistant unipolar depression, defined in this survey as a depressive episode meeting *DSM-5* criteria for major depressive disorder that has not remitted with adequate trials of 2 or more antidepressant medications. Eighty-two percent (n = 88) of clinics report prescribing maintenance ketamine treatment. Of these clinics, 68% (n = 59) report that a typical maintenance course is greater than 6 months, and 43% (n = 38) report that a typical maintenance course is greater than 12 months. Response data from all survey questions directly related to pregnancy or reproduction are detailed in Table 1.

Informed Consent Documents

Search engine queries returned a total of 70 publicly available informed consent documents from US-based ketamine clinics across 33 states, of which 38.5% (n = 27) of these do not include any language about pregnancy or risk of fetal ketamine exposure. Of the 61.4% (n = 43) that do mention pregnancy, 27% (n = 19) explicitly state there are potential risks related to fetal exposure. The remainder state that pregnancy is a reason for exclusion from ketamine treatment or that ketamine use during pregnancy is "generally not recommended." Sixteen percent (n = 11) mention the option or requirement to obtain a pregnancy test and 14% (n = 10) include a recommendation for contraception use.

Retrospective Medical Record Review

A cohort of 24 patients meeting inclusion criteria was identified. These patients ranged from 24 to 49 years of age with an average age of 32 years. For all patients in this

Table 1.

Survey of Pregnancy Testing, Contraception, and Informed Consent Practices

Standard pregnancy testing process (n = 105)	77.14% yes (n = 81)	22.86% no (n = 24)
Screening is performed prior to starting treatment	34.28% (n = 36)	
Testing is offered prior to starting treatment	22.86% (n = 24)	
Testing is required prior to starting treatment	9.52% (n = 10)	
Testing is required prior to starting and during treatment	10.48% (n = 11)	
Verbal informed consent process (n = 103)		
Pregnancy is not discussed	5.82% (n = 6)	
A general verbal recommendation to avoid pregnancy is given	46.6% (n = 48)	
Patients are verbally informed of specific risks related to exposure during pregnancy	47.57% (n = 49)	
Written informed consent documentation (n = 103)	Survey responses (n = 103)	Online documents (n = 70)
Language about pregnancy is not included	7.76% (n = 8)	38.5% (n = 27)
A general recommendation to avoid pregnancy is included	50.48% (n = 52)	61.42% (n = 43)
Language about specific risks related to exposure during pregnancy is included	41.74% (n = 42)	27.14% (n = 19)
Contraception counseling (n = 102)	26.47% yes (n = 27)	73.53% no (n = 75)
A recommendation to prevent pregnancy is given, but contraception is not discussed	12.75% (n = 13)	
Specific recommendations about pregnancy prevention are made	11.76% (n = 12)	
Contraception use is required during treatment	1.96% (n = 2)	

cohort, a pregnancy test was obtained prior to the first infusion and repeat testing was done weekly for the remainder of the treatment course (or prior to subsequent infusions if the dosing frequency was less than weekly). Contraception use was documented in 50% (n = 12) of these patients. None of the patients tested positive for pregnancy; however, 1 patient sought emergency contraception after unprotected sexual intercourse during the initial course of twice-weekly IV ketamine infusions.

DISCUSSION

The use of subanesthetic ketamine is becoming increasingly common in psychiatric practice given emerging evidence for efficacy and safety in treating a variety of mental health conditions. The potential effects of ketamine during pregnancy and fetal development, however, are not well understood, and there is limited guidance available about how clinicians should manage reproductive concerns during a course of ketamine treatment. To better understand current practices related to reproduction, an online survey was sent to over 450 outpatient ketamine clinics nationwide. The results of this study indicate a need for increased awareness of reproductive risks in the context of ketamine treatment for psychiatric illness. Clinics surveyed reported collectively treating over 7,400 individual patients with ketamine per month and estimated that a third of these patients were premenopausal biological females. These clinics represent a relatively small sample of approximately 500–750 ketamine clinics in the United States, thus a substantial number of women in the United States are receiving ketamine for psychiatric illness at any given time, and many have the potential to become pregnant during treatment.[28] Consequently, the risk of fetal ketamine exposure is an increasingly important public health concern that warrants attention and awareness.

Over 80% of clinics surveyed reported prescribing long-term or maintenance ketamine regimens. Of these clinics, over 60% estimate their average maintenance course duration as longer than 6 months and 44% as greater than 12 months. A recent study evaluating the long-term safety and efficacy of intranasal esketamine maintenance treatment for TRD demonstrated a generally sustained antidepressant effect without significant adverse events.[7] While these findings are not necessarily generalizable to other ketamine formulations or routes of administration, these data support the idea of maintenance ketamine use for TRD, and a large portion of clinics are utilizing ketamine as a maintenance treatment in clinical practice. Though potentially beneficial for psychiatric conditions, long-term ketamine use amplifies the possibility of fetal exposure over time. This risk is compounded as the likelihood of pregnancy increases in the context of psychiatric symptom remission with ongoing ketamine treatment.[29] This is distinctly highlighted by the requirement for emergency contraception use during a brief treatment course within the small patient cohort included in this retrospective review. While pregnancy may be relatively uncommon in the context of a short course of ketamine treatment for acute depressive symptoms or active suicidality, the potential for pregnancy should be more carefully considered in the maintenance phase of treatment.

As ketamine treatment becomes more widely available, broadly prescribed, and increasingly used as a maintenance therapy, there is an increasing need to inform patients with the potential to become pregnant about the risks of fetal exposure and to provide the necessary guidance to enable patients to make informed choices about their reproductive

Table 2.

Summary of Recommendations

Informed consent:

- A recommendation to avoid pregnancy for the duration of the ketamine treatment course should be discussed.
- Patients should be informed of the risks of fetal ketamine exposure including possible impact on neurodevelopment in addition to other, undetermined outcomes.
- Informed consent documentation should reflect this recommendation and include specific language about fetal ketamine exposure.

Testing:

- Prior to starting a course of ketamine treatment, pregnancy testing should be strongly recommended for all patients with the potential to become pregnant.
- Individual likelihood of pregnancy should be reassessed actively during the course of ketamine treatment, and repeat pregnancy testing should be recommended at an appropriate interval based upon a patient's individual risk.
- The absence of pregnancy should be confirmed prior to starting ketamine treatment for patients that were at a high risk of becoming pregnant in the 2–3 wk prior to evaluation.

Contraception:

- The need for ongoing pregnancy prevention should be discussed with all patients that could become pregnant, especially in cases involving long-term maintenance ketamine treatment.
- The use of a highly reliable contraceptive method should be strongly recommended, and appropriate consultation should be sought for this if needed.

Reproductive planning:

- Reproductive goals should be discussed with patients, and plans for pregnancy should be taken into account when considering maintenance ketamine treatment.
- If a patient becomes pregnant or chooses to attempt to become pregnant, ketamine treatment should be safely discontinued and, if needed, the patient transitioned to an alternative treatment that is appropriate for use during pregnancy.
- Specialized psychiatric consultation may be necessary in these cases as there can be significant complexity in managing psychiatric illness in the perinatal period.

health. Some proposed recommendations for clinical practice are detailed in Table 2. Patients should be advised of the risks of fetal ketamine exposure, including possible impacts on neural development in addition to the potential for other, undetermined outcomes given the lack of human study data. Currently, there is significant variability regarding pregnancy screening, testing, and counseling in the context of psychiatric treatment with ketamine as evidenced by survey responses summarized in Table 1. Established guidelines for managing reproductive concerns when using other teratogenic medications such as valproate may provide a framework for prescribing ketamine treatment to women with childbearing potential.[30] This typically includes testing for pregnancy in all patients with the ability to become pregnant prior to starting a potentially teratogenic treatment to ensure patients are not exposed during a time in which they may not yet know they are pregnant followed by recurrent testing during the treatment course at an appropriate interval based upon the patient's individual likelihood of becoming pregnant. This has the potential to vary substantially during the treatment course, especially for women who may be receiving long-term maintenance ketamine. It is important to note that false-negative results are possible during the earliest stages of conception, so this should be considered in patients who may have been at risk of becoming pregnant during the 2–3 weeks prior to starting treatment. Prescribers should continue to actively reassess reproductive risk throughout the treatment course. Pregnancy prevention should be discussed, and it may be necessary to recommend that patients consult with their primary care physician or obstetrician/gynecologist to start a highly reliable form of contraception before prescribing ketamine treatment.[31] The results of our investigation revealed that only about a quarter of clinics currently discuss the need to prevent pregnancy during a course of ketamine treatment, and fewer than 15% actually recommend patients seek relevant consultation for this. Additionally, only half of the patients in the cohort were confirmed to be actively using contraception. Up to 85% of sexually active women who are not using contraception and approximately 25% of women using less reliable methods will become pregnant within 1 year.[32] As such, ketamine prescribers have a responsibility to ensure that patients are aware of the need to prevent pregnancy during treatment and to provide appropriate counseling that enables patients to do so effectively. Reproductive plans should be discussed with patients, particularly when considering if maintenance ketamine is an appropriate treatment option. Prior to attempting to become pregnant, ketamine may need to be carefully and thoughtfully discontinued, and patients transitioned to an alternative treatment that is safe to use during pregnancy. Consultation with a perinatal psychiatry specialist may be necessary given the physiological and psychological complexities of managing psychiatric illness during the high-risk peripartum period.[33]

Additional research is needed to further determine the potential teratogenic effects of prenatal ketamine exposure. The Massachusetts General Hospital National Pregnancy Registry for Psychiatric Medications aims to evaluate the safety of various psychotropic medications during pregnancy, and patients with known exposure to ketamine should be informed about the option to enroll.[34] Given the current lack of evidence for safety, prevention of fetal ketamine exposure should be a priority for all prescribers who utilize this modality in treating psychiatric illness. Ketamine is an effective and potentially life-saving treatment for a variety of psychiatric indications; however, reproductive risks need to be considered during the course of treatment. The results of this study highlight that the risk of fetal ketamine exposure is underappreciated, and practices related to testing, informed consent, and counseling are often insufficient. This discrepancy has potentially serious implications for public health. There remains an urgent need for evidence-based practice guidelines that emphasize reproductive concerns and provide guidance in clinical practice. Reproductive risks can be mitigated by implementing screening, testing, and counseling practices to minimize potential in utero ketamine exposure.

Limitations

There are several limitations of this study, most notably the inherent limitations to survey research including sampling and response biases. Our survey was distributed to all ketamine clinics with a publicly available email address, so clinics without contact information were excluded from participation. Of clinics contacted, 26% completed the survey, but it is not known to what degree collected responses are generalizable to the entire surveyed population or the population of ketamine clinics in the United States as a whole. Likewise, publicly available informed consent documents were reviewed; however, it is unclear if these are truly representative of informed consent practices outside this relatively small sample of ketamine clinics. It seems unlikely that the presence or absence of a published contact email address and/or an informed consent document would correlate with significant differences in clinical practice, but this cannot be ruled out. It is also important to note that the cohort of patients identified for retrospective medical record review was fairly small, which may again limit generalizability.

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