Acute Aggression After Progesterone Discontinuation in a Young Woman

Mujeeb U. Shad, MD, MSCS[a,b,c,*]

The psychiatric effects of progesterone and its primary metabolite allopregnanolone are well-documented in anxiety,[1] premenstrual syndrome, dysmenorrhea,[2] and postpartum depression.[3,4] However, the clinical evidence for progesterone's role in behavioral aggression is scarce. This report describes the first case of acute aggression in a young woman after the discontinuation of a subdermal etonogestrel implant and resolution of aggression after the initiation of depot medroxyprogesterone acetate (DMPA).

Case Report

The patient, a 23-year old black woman with severe posttraumatic stress disorder (PTSD), unspecified bipolar disorder, and a history of alcohol use disorder, was admitted to a psychiatric facility to manage extreme agitation and suicidal thoughts precipitated by excessive alcohol intake. Medications at admission included fluoxetine 60 mg/d, prazosin 2 mg/d, perphenazine 8 mg 2 times/d, and divalproex sodium 500 mg 2 times/d with therapeutic levels (ie, 91 mcg/mL). Since the patient developed significant extrapyramidal symptoms and hyperprolactinemia, she was gradually cross-titrated from perphenazine to quetiapine 300 mg at bedtime with resolution of both adverse effects as well as symptom stabilization. However, a couple of weeks before the patient's discharge, the progesterone contraceptive implant, etonogestrel (Nexplanon), was secretly removed by the patient so that she could become pregnant despite cautions against teratogenic effects of divalproex sodium. Within 2 days, the patient became extremely aggressive toward staff and peers for 3 days despite the frequent use of as-needed antipsychotics and sedatives (Table 1). But, the patient did not exhibit pressured speech, increase in goal-directed activity, grandiosity, decreased sleep, or flight of ideas. After discovering the implant removal, the patient was started on DMPA (Depo-Provera) to prevent future nonadherence. She stabilized within 3 days and was discharged from the state psychiatric facility a week later after a 3-month hospitalization (Table 1).

Discussion

This is the first case, to my knowledge, of acute aggression after 2 days of discontinuing an etonogestrel implant followed by aggression resolution within 3 days of starting DMPA. This onset of action is consistent with the time DMPA requires for its peripheral effects[5] (Table 1). Since progesterone can easily cross the blood-brain barrier, the appearance of peripheral effects in 2 days may coincide with the central effects. The half-life of etonogestrel is 25 hours,[6] which means that the etonogestrel levels may decline more than 50% in 2 days, further explaining peripheral changes within 2 days of progesterone discontinuation.[5] Of note, the implant's removal did not result in menstruation, which rules out behavioral dysregulation due to hormonal changes other than progesterone.[7,8] Although the mechanisms underlying aggression are not clear, progesterone's discontinuation may have resulted in behavioral dysregulation due to loss of positive allosteric modulation of inhibitory γ-aminobutyric acid-A (GABA-A) receptors, which has been reported with progesterone's primary metabolite, allopregnanolone.[3,4] An increase in GABA activity dampens the glutamate excitotoxicity associated with behavioral aggression,[9] postpartum depression,[10,11] and psychosis.[12] Despite underlying bipolarity, therapeutic levels of divalproex sodium did not prevent the sudden onset of behavioral aggression in this patient, suggesting that allosteric modulation may differ from valproic acid's direct GABAergic effects. Thus, it is plausible that loss of potential mood stabilization with the contraceptive[13,14] may have precipitated aggression in this patient. A decrease in progesterone levels has also been associated with posttraumatic symptomatology and heightened intensity, as well as the duration of adrenergic response,[15] which may be relevant in this patient diagnosed with PTSD. Also, individuals with low plasma GABA levels are prone to develop PTSD after a traumatic experience.[16] Unfortunately, the progesterone level was not measured to support the findings in this case, which also could have helped to rule out any drug interactions. Etonogestrel is metabolized by the cytochrome P450 (CYP) enzyme system,[17] which does not metabolize any of the psychotropic medications prescribed to this patient except quetiapine.[18] However, it is counterintuitive to think that a potential increase in etonogestrel levels due to competitive inhibition by quetiapine contributed to behavioral dysregulation in this patient. A similar argument can be made with high-dose use

[a]Department of Psychiatry, University of Nevada, Las Vegas, Nevada
[b]Department of Psychiatry, Touro University Nevada, College of Osteopathic Medicine, Las Vegas, Nevada
[c]Department of Psychiatry, Valley Health Services, Las Vegas, Nevada
*Corresponding author: Mujeeb U. Shad, MD, MSCS, Valley Health System, Spring Mountain Hospital and Medical Center, 5400 South Rainbow Blvd, Las Vegas, NV 89118 (mujeebushad@gmail.com).

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Table 1. Temporal Relationship Between Extreme Aggression, Progesterone Events, Changes in Psychotropic Medications, and Psychiatric Symptoms[a]

Admission and Post Admission Days	Aggression Events	Progesterone Events	Changes in Psychotropic Medications	Psychiatric Symptoms
Admission at the state psychiatric facility	No aggression	Contraception with the synthetic progesterone contraceptive implant etonogestrel (Nexplanon)	Perphenazine 8 mg 2 times/d Fluoxetine 60 mg/d Prazosin 2 mg/d Divalproex sodium 500 mg 2 times/d	Anxious Agitated Flashbacks Nightmares Easy startle Guarded No bipolar symptoms No alcohol withdrawal, as alcohol use disorder was in early sustained remission
15 days	No aggression	Etonogestrel continued	Gradual cross-titration from perphenazine to quetiapine 300 mg at bedtime Addition of prazosin 2 mg/d Continuation of fluoxetine 60 mg/d and divalproex sodium 500 mg 2 times/d	Less nightmares Sleeping improved Less flashbacks Significantly less anxious Grooming improved Attending inpatient activities and groups
75 days	No aggression	Etonogestrel removed	Same medications	Same symptoms as at 15 days
77 days	New-onset extreme aggression	No contraception	Added IV haloperidol 5–10 mg with 2 mg of IV lorazepam every 4–6 h as needed No change in other medications	Same symptoms as at 15 and 75 days No new bipolar symptoms
80 days	Continued extreme aggression	Started depot contraceptive DMPA (Depo-Provera)	Added IV haloperidol 10 mg with 2 mg of IV lorazepam every 4 h as needed No changes in other medications	Same symptoms No new bipolar symptoms
83 days	Resolution of aggression	DMPA continued	Discontinuation of as-needed medications Quetiapine 300 mg at bedtime Fluoxetine 60 mg/d Prazosin 2 mg/d Divalproex sodium 500 mg 2 times/d	Significantly less anxiety No bipolar symptoms
90 days	Continued lack of aggression	DMPA continued	Quetiapine 300 mg at bedtime Fluoxetine 60 mg/d Prazosin 2 mg/d Divalproex sodium 500 mg 2 times/d	Stable enough to be discharged

[a]Substance or alcohol use did not play a role, as the patient was detoxed before admission to the state psychiatric facility.
Abbreviations: DMPA = depot medroxyprogesterone acetate, IV = intravenous.

of fluoxetine (ie, 60 mg/d) that can also inhibit CYP3A4[19] and may increase etonogestrel levels. In addition, during a 3-month hospitalization, sobriety makes alcohol a less likely contributor to aggression in this patient. Although the findings from this report are based on a single case and should be interpreted cautiously, clinicians should consider progesterone's psychiatric effects beyond contraception, especially in patients with complex psychiatric comorbidities.

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