

Update on Reproductive Safety of Psychotropic Medications Part I of an Interview with Lee S. Cohen, M.D.

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Currents: Dr. Cohen, does pregnancy affect the course of depression or bipolar disorder?

Cohen: When we started our service in the late 1980's, the prevailing notion was that pregnancy protected against risk for psychiatric disorder, and the prevailing recommendation was that women stop psychiatric medications during pregnancy, regardless of their history. Many clinicians believed that the hormonal environment of pregnancy protected women with psychiatric disorders, and some women did, in fact, report that they never felt better than while pregnant. In contrast, our clinical experience early on was that many women who had been taking either antidepressants or mood-stabilizers relapsed after discontinuing those medicines before or during pregnancy. Women with bipolar disorder in particular appeared to become ill very quickly, and our own data subsequently demonstrated high risk of relapse after abrupt discontinuation of mood-stabilizers.

We now have a clearer idea of what happens with respect to risk of major depression during pregnancy. Several studies, one done by the Iowa group, looked at the prevalence of depression in pregnant and non-pregnant women and found equivalent risk. That was one of the first prospective studies of prevalence of depression during pregnancy. Then, our group did the first prospective study of relapse of recurrent major depression during pregnancy in women with histories of major depression who had stopped their antidepressants around the time of conception. We found that 75 percent of them relapsed during pregnancy, with the majority of relapses occurring during the first trimester.

A parallel, collaborative study done by our group and the groups at UCLA and Emory found that among women with recurrent major depression who had stopped their antidepressants during pregnancy, half resumed treatment before the end of pregnancy. Given a woman's reluctance to take medication during pregnancy, we felt that a 50-percent rate of resuming treatment was probably an underestimate, and, in fact, it subsequently proved to be, with an even larger number of women relapsing during pregnancy, but not going back on medicine. That is a concern, because some data suggest that untreated depression during pregnancy per se is associated with higher rates of poor perinatal outcome, lower APGAR scores, higher rates of preterm labor, and other types of obstetrical complications. Therefore, while we remain concerned about using or reintroducing medication during pregnancy, we appreciate the risks of untreated disease--both those associated with depressive symptoms and depression-related behaviors, such as not eating or not sleeping or using illicit substances, and those associated with depression per se that adversely impact fetal wellbeing.

With respect to women with bipolar disorder, Adele Viguera in our group recently published a study of bipolar women who had discontinued lithium proximate to becoming pregnant. That study found a very high rate of relapse in the first six months after lithium discontinuation, and, in fact, the survival curve was virtually superimposable on the survival curve of a non-pregnant historical control group who had discontinued

lithium. The data on unipolar women who discontinue antidepressants and bipolar women who discontinue mood-stabilizers suggest that relapse is a very common and that we can no longer accept the clinical lore that pregnancy has protective effects. We have to presume that clinical lore misinforms clinical practice in that respect.

Currents: What about the recent study by Paul Grof and colleagues (*Journal of Affective Disorders* 61(1-2):31-39, 2000; Ed.) reporting fewer and less severe affective episodes in a sample of women with bipolar I disorder?

Cohen: In that study, women had relatively remote histories of bipolar illness. They had been treated in the past for an acute episode of bipolar disorder and had been well for a long duration while medication-free. Accordingly, Grof et al's sample was very different from our sample of recurrently ill bipolar women who discontinued mood stabilizers close to the time of conception. The course of bipolar disorder may be highly variable as a function of the history of illness.

Currents: What about the course of disorders other than unipolar major depression and bipolar disorder during pregnancy?

Cohen: Our clinical experience and data from studies of panic disorder and obsessive-compulsive disorder suggest that rates of relapse during pregnancy are high after discontinuation of anti-panic or anti-obsessional medications. The same appears true for women with chronic psychotic disorders who discontinue antipsychotics. And, if that is so, it becomes critical for clinicians to be ready with a treatment plan or algorithm as they counsel women of childbearing age who want to become pregnant and come for advice about what to do. We must also be informed when choosing antidepressants and other psychiatric medications for women of childbearing age who are **not** planning to become pregnant, because data over the last decade indicate that half of all pregnancies in the U.S. are unplanned. We should therefore consider the reproductive safety of psychiatric medications when prescribing for all women in their childbearing years, because a significant proportion of them will become pregnant, deliberately or inadvertently.

Currents: What is the current best information about the safety of psychiatric medications during pregnancy?

Cohen: It is useful to think about reproductive safety across three domains: risk of organ malformation, risk of neonatal toxicity, and risk of longer term neurobehavioral sequelae. We have the most data about risk of organ malformation, or teratogenesis. Looking at reproductive safety class by class, the data are reasonably consistent for the typical antipsychotics, in that they show an absence of increased risk of major malformations associated with first-trimester exposure. We do not have good data yet about the reproductive safety of the atypical antipsychotics. An olanzapine registry was started recently, but it will be some time before we have useful information about olanzapine or other atypical antipsychotics. We clearly need that information, because the atypicals are being used across a wide spectrum of disorders associated with higher fertility rates than that of schizophrenia. For example, the use of atypical antipsychotics is increasing in relatively high functioning women with mood disorders, anxiety disorders, and personality disorders.

Another issue with respect to prescribing antipsychotics is that the atypical drugs are generally less likely to induce hyperprolactinemia, which commonly occurs during treatment with typical antipsychotics and impairs fertility by disrupting hypothalamic-pituitary-gonadal function. Clozapine, olanzapine, and quetiapine (and, it appears, ziprasidone) are prolactin-sparing, and women taking those medications are probably more likely to become pregnant than are women taking typical antipsychotics. Accordingly, it becomes more important for them to use effective contraception if they do not wish to become pregnant.

Currents: Among the atypical antipsychotics, risperidone has been reported to induce significant hyperprolactinemia, has it not?

Cohen: It has. The data strongly suggest that risperidone is at least as likely to induce hyperprolactinemia as are typical antipsychotics, and may be more likely to. In a preliminary study, we compared prolactin concentrations in women taking haloperidol, risperidone, and olanzapine, and found not only a higher risk of hyperprolactinemia in risperidone-treated women than in olanzapine-treated women, but also a two-fold higher risk of hyperprolactinemia in risperidone-treated than in haloperidol-treated women.

Currents: How powerfully does hyperprolactinemia affect fertility?

Cohen: The best marker for intact hypothalamic-pituitary-gonadal function or intact reproductive endocrine function is not the prolactin concentration, but rather the menstrual history. Some patients have significantly elevated plasma prolactin concentrations and intact menstrual function, and the menstrual function (as indicated by the menstrual calendar) is the more sensitive marker for intact hypothalamic-pituitary-gonadal function. There is no better or more specific marker for intact female reproductive endocrine function than a regular menstrual cycle.

Currents: Yet many other things can affect the menstrual cycle.

Cohen: Absolutely, but clinicians sometimes have the misimpression that hyperprolactinemia in and of itself has powerful predictive value. That is not necessarily so. For example, in our study, many women with moderate hyperprolactinemia had normal menstrual function and many women with abnormal menstrual function had serum prolactin concentrations in the normal range.

Currents: Is hyperprolactinemia over a long term a risk factor for osteoporosis?

Cohen: The data suggesting clear-cut, end-organ sequelae associated with hyperprolactinemia are weak. One can reasonably speculate that hyperprolactinemia, so far as it reflects blunted ovarian function, might convey risk of long-term sequelae associated with hypoestrogenic states such as menopause, but no convincing prospective data have yet supported that. The studies have not been done, nor have studies about whether antipsychotic-induced hyperprolactinemia is a risk factor for development of breast cancer.

Currents: Are the aliphatic or piperazine phenothiazines as safe during pregnancy as the high-potency, piperazine phenothiazines, butyrophenones, or thioxanthenes?

Cohen: High-potency antipsychotics have been the preferred agents, because some of

the early data indicated a trend toward higher rates of malformations in children exposed *in utero* to low-potency antipsychotics. I consider the low-potency agents relatively contraindicated during pregnancy. The issue doesn't come up much now, because we tend to use high-potency agents. Another reason why we tend to avoid low-potency agents, such as chlorpromazine and mesoridazine, is that their anti-adrenergic and anticholinergic effects may cause hypotension and tachycardia.

Currents: Do you favor a particular atypical antipsychotic for use during pregnancy?

Cohen: When treating psychiatrically ill pregnant women, you treat the patient where you find her. What I mean by that is that contraindications tend to be relative. We have used clozapine or olanzapine in pregnant patients with refractory bipolar disorder or refractory psychotic illness that had not responded to medicines for which we had better data supporting reproductive safety. The reason we have done so is because the more important issue in those patients has been to avoid a higher risk of relapse associated with reverting to a safer drug. So, although it is not our preference to use medicines for which we do not have good reproductive safety data, we sometimes do it for overriding clinical reasons. We approach patients on a case-by-case basis, weighing risk of exposure against risk of relapse.

Currents: Suppose you had a pregnant patient that you intended to treat with an atypical antipsychotic (because of a prior history of sensitivity to extrapyramidal adverse effects, for example), and you had no reason to believe that risperidone or olanzapine would be more or less effective than the other for psychotic or manic symptoms. Would you choose olanzapine because it is less likely to raise serum prolactin?

Cohen: Yes, and I would probably also do so because of some reports suggesting that risperidone may be more likely than olanzapine to induce extrapyramidal adverse effects.

Currents: Ziprasidone also is prolactin sparing, is it not?

Cohen: It is supposed to be, but we have no reproductive safety data on ziprasidone. The database with the other atypicals is extremely small as well, but if you are going to use an atypical antipsychotic in a woman who is pregnant (for the same reasons that you would use an atypical antipsychotic in a woman who is not pregnant), it would be better to use a medication for which we have the most data supporting safety.

Currents: Ziprasidone might be an advantage where weight-neutrality is desirable.

Cohen: I would be concerned about using a medicine for which we have no reproductive safety data, especially since there are other ways to modulate weight-enhancing effects of atypical antipsychotics and other psychiatric medications. Weight-neutrality would not prompt me to prescribe a medication for which there were no data about reproductive safety. On the other hand, because precipitous weight gain during pregnancy is clinically significant, a drug's likelihood to promote weight gain should be included in risk/benefit considerations during pregnancy.

Currents: Do we have reproductive safety data on lamotrigine, which is reported to be weight-neutral, or on topiramate, which has been reported to promote weight loss?

Cohen: An anticonvulsant registry here at the Massachusetts General Hospital collects cases of first-trimester exposure to the anticonvulsants that we use for bipolar disorder, but at this point, we have too few cases to indicate safety or lack of safety of gabapentin, lamotrigine, or topiramate. At this point, when it comes to mood stabilizers, we have the most data about lithium and sodium valproate.

Currents: What is the most recent thinking about the risk-benefit calculus of using lithium during pregnancy?

Cohen: We evaluated that in 1994 in the context of earlier concerns of the Lithium Registry of Babies about risk of cardiovascular malformations associated with first-trimester exposure to lithium. When we revised that risk, we estimated that women who used lithium during the first trimester had a 0.05 percent-chance of having a child with Ebstein's anomaly. Because risk of relapse was so high after discontinuation of lithium during pregnancy, we started to treat our pregnant bipolar patients with lithium more aggressively at that time. We became more willing to continue lithium during the first trimester in bipolar patients with recurrent disease. We felt that it was safer to leave the patient on lithium, or, at a minimum, give her information about the risk of relapse, compared to the risk for having a child with a cardiovascular malformation. Studies have not supported an overall increased risk of non-cardiovascular malformations from first-trimester lithium exposure; what is increased is the risk of cardiovascular malformations. Again, that risk is relatively small, and many women may want to take it, particularly since there is a 50-percent risk of relapse within six months of lithium discontinuation.

Currents: When a patient wants to discontinue lithium or other mood-stabilizer, when should she do it?

Cohen: Some women whom we counsel stay on lithium while they are trying to get pregnant because the time it takes to conceive is highly variable. The clock to relapse starts running when our patients stop their mood-stabilizer; other women opt to discontinue medication when they become pregnant. That is safer with lithium than with valproic acid, because the heart forms at approximately nine weeks of gestation. The gestational age of the fetus is four weeks at the time of the first missed period, so the patient could taper off of lithium, even over a ten-day to two-week period, and still be on the "front" side of the critical window when the heart forms.

The situation with valproic acid is different. Valproic acid exposure during the first trimester is associated with a five- percent risk of neural tube defects--one-hundred-fold greater than that of Ebstein's anomaly associated with first-trimester lithium exposure. Many women now are treated with valproic acid as first-line therapy for acute or maintenance treatment of bipolar disorder, and one must question, given the high rate of unplanned pregnancy in the U.S., whether it should remain an appropriate first-line therapy for bipolar women of childbearing age. The issue is made more critical by the narrowness of the window within which valproic acid can be safely discontinued after conception. For example, if a woman documents pregnancy early, say at six or seven weeks of gestation, which is when most women document their pregnancies (not the day after they are late for a period), she is beyond the point when neural crest formation is complete. The "teratogenic window" has closed by the time she knows that she is

pregnant. With lithium, a woman has more time to discontinue treatment after documenting pregnancy. This is a critical point, because we see many women with histories of multiple relapses who want to stay on mood stabilizers while they are trying to conceive. Yet, even with the best efforts to document pregnancy early, it is difficult to do so and then discontinue valproic acid before the critical period of neural crest formation.

Currents: What, then, do you recommend for women who are taking valproic acid and want to conceive?

Cohen: If they have never taken lithium (and many patients have not) and wish to continue treatment because of high relapse risk, we will switch them from valproic acid to lithium. We often manage patients who have severe, recurrent illness with lithium and sometimes a little bit of a high-potency antipsychotic during the first trimester of pregnancy. We do that as an alternative to using drugs such as valproic acid, lamotrigine, or topiramate.

Currents: Is valproic safe during the second and third trimesters?

Cohen: We don't have much data on valproic acid in the later trimesters. However, colleagues in neurology do use valproic acid during the second and third trimesters in women with epilepsy.

Currents: Carbamazepine is being used less than previously, but a derivative, oxycarbazepine (Trileptal), has been introduced for treatment of epilepsy. Some preliminary data suggest that oxycarbazepine might have mood-stabilizing properties and have less robust enzyme-inducing properties than carbamazepine. Do we know anything about its safety in pregnancy?

Cohen: There are no data about it yet.

Currents: Is the neural tube malformation associated with carbamazepine similar to that associated with valproic acid?

Cohen: Yes, but there is a one-percent risk of spina bifida in children exposed to carbamazepine during the first trimester. Carbamazepine is therefore five-fold safer than valproic acid in that respect. Even so, both valproic acid and carbamazepine must be used with great caution in women of childbearing age.

Currents: Do lithium or valproic acid dosages or blood concentrations affect risk of teratogenicity?

Cohen: There is no clear-cut relationship of dosages or blood concentrations to organ malformation associated with lithium, valproic acid, or carbamazepine. It would seem intuitive that more would be worse, but that turns out not to be the case. The reason that that is clinically relevant is because once you decide to use a psychiatric medication during pregnancy, you should use it at a dosage that gets and keeps the patient well. We often see undertreatment with psychiatric medications during pregnancy because of a presumption that lower dosages are safer. That isn't the case, because undertreatment represents a failure of the risk-benefit decision process.

Currents: So then, we can't say that someone who is taking lithium for antidepressant augmentation and has a blood level of 0.4 meq/L is less likely to have a baby with Ebstein's anomaly than somebody who is taking lithium for bipolar I disorder and has a blood level of 1.1 meq/L.

Cohen: Right, and even in animal models where lithium has been given in very high doses that produce very high plasma levels, the risk of cardiovascular malformations has not been increased.

Currents: What is your assessment of a possible association between valproic acid and polycystic ovary syndrome?

Cohen: My read on that is that we need data from larger, better characterized patient samples before we can make definitive conclusions about the risk of polycystic ovary syndrome and exposure to valproic acid. Unfortunately, the original study by Isojarvi and colleagues was confounded, and the studies that have followed have been small and inconclusive. Polycystic ovarian morphology is not the same as polycystic ovary syndrome: One third of women in the general population have polycystic ovarian morphology when studied with ultrasound. Polycystic ovary syndrome is associated with clinical correlates of hyperandrogenism, and that has not been a consistent diagnostic criterion in the Finnish studies.

Currents: Some small studies in women with bipolar disorder have not found an association between valproic acid treatment and polycystic ovary syndrome.

Cohen: That's right, and we need data from a larger study, which in fact is being done now in the U.S. as part of the STEP bipolar program, which is the NIMH multi-center bipolar study. The study on polycystic ovary syndrome is being coordinated by Hadine Joffe at our center, where we are looking at a large number of women with bipolar disorder. The patients who typically have been described in the literature have been women with epilepsy, which must be assessed as a possible confound. It will be a while before we have answers.

Currents: Would it be fair to say at this point, then, that the well-documented risks of undertreated bipolar disorder would outweigh a potential risk of polycystic ovary syndrome in valproic acid-treated women?

Cohen: Yes, and I would go a step further in adding that unplanned pregnancy in valproic acid-treated women is a greater concern to me than risk of developing polycystic ovary syndrome.

Currents: What about safety of psychotropic medications during labor and delivery?

Cohen: There has always been concern about using not only SSRI's but also other antidepressants and other psychiatric medications during the time of labor and delivery. That concern arose from anecdotal reports in the 1970's of tremulousness, jitteriness, and difficulty feeding in babies born to mothers taking tricyclic antidepressants. There was, for example, one case of urinary retention in a child whose mother was using nortriptyline at the time of labor and delivery. Those reports raised concern about whether using psychotropic medications put children at risk for what was termed "neonatal toxicity." In fact, there have been very few reports of so-called "neonatal

toxicity" associated with maternal use of psychiatric medications over the last ten years. With respect to SSRI's, there was a report of tremulousness and jitteriness in the baby of a woman who was using paroxetine during pregnancy, and there has been concern as well about the use of fluoxetine during the peripartum period. Additional concern about fluoxetine was raised by a study by Chambers and colleagues from San Diego, which suggested that the use of fluoxetine during late pregnancy and into labor and delivery was associated with higher rates of poor perinatal outcome than occurred in babies of women treated with fluoxetine early in pregnancy. Unfortunately, that study was flawed because the children were born at multiple hospitals and the raters who defined toxicity were not blind to maternal treatment status. The specific finding was that children whose mothers used fluoxetine late in pregnancy had higher rates of special-care nursery admissions than did children whose mothers had used fluoxetine early in pregnancy. The authors also described a syndrome of so-called poor neonatal adaptation, which was really a series of non-specific, transient problems in the newborn related to color, tone, and other problems. We were struck by that finding, because we had not heard about higher rates of special-care nursery admissions in babies born to our patients who had used fluoxetine in late pregnancy. We therefore looked at the patients that we had followed throughout pregnancy and into the postpartum period, and we published our results last year in **Biological Psychiatry**. Our study design was similar to that of Chambers and colleagues, and indeed we did find similar rates of special-care nursery admissions. Nevertheless, the indications for special-care nursery admissions that we observed could not be convincingly attributed to fluoxetine exposure. These were transient special-care nursery admissions, which typically did not last for more than 24 hours; in many cases, they were for only one to three hours; children almost uniformly went home with their mothers within the short time frame of standard postpartum discharge planning.

I think the take home message at this point is that anecdotal reports may suggest a small risk of a transient syndrome of tremulousness and jitteriness in children whose mothers take antidepressants during the peripartum period. One needs to remember, however, that there may be a more significant risk associated with lowering the antidepressant dosage or discontinuing an antidepressant late in pregnancy. Depression during pregnancy remains the strongest predictor of postpartum worsening of psychiatric illness.

Currents: And yet the blood volume shrinks after delivery, presumably increasing antidepressant blood levels.

Cohen: That is true. The blood volume shrinks, and that would imply some relationship between plasma level and both response and even prophylactic benefit during the postpartum period. Yet, no data clearly support that. Reduced plasma volume after delivery most often has been described in lithium-treated patients during the acute postpartum period. The issue may have been oversimplified, though, because shifts in plasma volume are not necessarily unidirectional and do not necessarily occur in a linear fashion. The postpartum period is more a period of hemodynamic flux than uniform hemoconcentration. What you suggest may be correct, and there may be a relative increase in plasma antidepressant concentrations or potentially effective delivered dose during the postpartum period, but that has not been formally or systematically studied.

Our concern has always been that either lowering or discontinuing treatment just before a woman enters a period of risk seems to be less than thoughtful care. We

therefore maintain antidepressant treatment at the dosages to which patients responded during pregnancy, so that we can maximize the likelihood that they will remain euthymic across labor and delivery and into the postpartum period. Responding to the anecdotal reports of tremulousness a decade ago, we pondered whether it might be prudent to lower antidepressant dosage or discontinue antidepressants and then reintroduce them postpartum. Unfortunately, when we did that, we encountered so many clinical problems with recurrence or worsening of depression that we abandoned the practice. The practice of tapering or discontinuing psychiatric medication before labor and delivery should be reexamined because it puts mothers and their babies at risk.

Currents: Not only from loss of therapeutic effect, but perhaps from antidepressant withdrawal or discontinuation symptoms.

Cohen: Yes, potentially with respect to discontinuation symptoms, but primarily with respect to putting mothers at risk for puerperal illness.

Currents: Do you feel the same way about continuing lithium at the time of labor and delivery?

Cohen: We do now, but as recently as five to ten years ago we recommended either that lithium dosage be reduced by 30 percent or that lithium be discontinued in bipolar women approaching term. Again, an anecdotal literature describing so-called "neonatal toxicity" drove those recommendations, and our subsequent experience and data indicated a very low risk of anything resembling neonatal toxicity in the acute postpartum period. Since bipolar women are at a five-fold higher risk for postpartum depression than are women who do not have affective disorder, it no longer seems appropriate to withdraw treatment just before a woman delivers. Doing so would likely drive up the risk for postpartum disease in an already vulnerable population. We have demonstrated the value of postpartum prophylaxis now in several studies, and it is clear that prophylaxis, at least with lithium in bipolar women around the time of labor and delivery, dramatically lowers risk for postpartum relapse. So, as with antidepressants, we have abandoned the practice of lowering lithium dosage or discontinuing lithium around the peripartum period.

Currents: What about someone who chooses to discontinue medication during pregnancy and has done well? Do you routinely recommend resumption of lithium or other mood stabilizer after delivery, knowing that the postpartum period is associated with high risk of relapse?

Cohen: We typically share with the patient the data suggesting that bipolar women are at high risk for postpartum disease. For women with more mild disease, we may wait until after the acute postpartum period (the first 24 to 48 hours) before resuming treatment. For women with severe, recurrent bipolar I disorder who stop lithium during pregnancy, we typically recommend a resumption of lithium at 36 weeks of gestation, even if they are doing well without lithium at that point. We do this because we have seen severe relapses in those patients when we have waited until 24 to 72 hours into the acute postpartum period. We do not have a lot of systematic data about this, but our experience has been that earlier prophylaxis appears to reduce risk of puerperal illness in bipolar women.

Currents: What about safety of benzodiazepines during pregnancy?

Cohen: There are several important issues with benzodiazepines during pregnancy. First, there is the issue of using them during the peripartum period. As with many other psychiatric medications, the recommendation has been to reduce dosage or discontinue treatment proximate to delivery. Again, that recommendation derived from anecdotal reports suggesting a greater risk of so-called "floppy babies" or "hypotonic babies" born to mothers taking benzodiazepines during labor and delivery. There was also a case of neonatal apnea associated with maternal use of high doses of clonazepam and a report of benzodiazepine withdrawal symptoms in a child whose mother was being treated with a high dosage of alprazolam. We have found it very difficult to lower the dosage of benzodiazepines such as clonazepam around the time of labor and delivery. As with our patients who had mood disorder, we found that our patients with anxiety disorders developed severe worsening of symptoms postpartum when we reduced benzodiazepine dosage or discontinued benzodiazepines around the time of labor and delivery. Also, when we looked at perinatal outcome in a small series of women whom we had treated throughout pregnancy with clonazepam daily dosages of 0.5 to 3.5 milligrams, we saw nothing that looked even remotely like the anecdotally described hypotonia or apnea or so-called "floppy baby syndrome." You nevertheless must remain alert to the possibility that there may be subgroups of newborns, perhaps premature infants or infants with immature hepatic metabolism (babies with hyperbilirubinemia, for example) who may be vulnerable to transient neonatal effects. But, as we have seen more and more patients over the years, we have decided to maintain treatment across the peripartum period to modulate risk of postpartum worsening of anxiety. As with depression, nothing predicts postpartum anxiety more strongly than anxiety during pregnancy.

(To be continued)