Antipsychotic Medications and Fertility

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As a colleague in family practice writes, "Often the family physician has to deal with lack of cooperation from patients [with schizophrenia] when they are asked to use common forms of contraception. [As a contraceptive measure for such patients,] some family physicians rely on the infertility secondary to hyperprolactinemia caused by traditional antipsychotic agents" (1). As this quote implies and an evolving literature suggests, some clinicians perceive neuroleptic-induced amenorrhea as a desirable form of surreptitious contraception, with or without patients' comprehension of this potential "side effect."

This view may be grounded in medical paternalism, but may also be supported by studies showing that the reproductive patterns of both male and female patients with schizophrenia tend to be more chaotic than those of the general population. For example, female patients with schizophrenia have more births that are unplanned and more abortions and are more likely to lose custody of children compared with women in control groups with no mental illness or nonpsychotic mental illness (2,3). Patients with schizophrenia also have been less accepting of common contraceptive methods than have other groups (4).

Fertility among patients with schizophrenia has long been a focus of clinical and research interest. Studies done before the advent of neuroleptic medications in the 1950s attempted to characterize somatic and genetic effects of schizophrenia. Although these studies of case registries and census data sought to demonstrate a reduction in fertility as a marker of poor genetic "fitness," no consistent primary limitation of fertility was found (4). Rather, low birth rates among patients were thought to be secondary to social and cultural factors, such as low marriage rates (then considered a barrier to reproduction), high divorce rates, and long-stay hospitalization during the most fertile years.

Since the 1970s, psychiatric practice has evolved from an institutional to a community focus. Arguably, social stigma surrounding mental illness has lessened. Childbirth outside of marriage is commonplace. These factors predict increased fertility rates among persons with serious mental illness. More recent controlled studies in community settings show minimal impairment of fertility (ability to conceive) and fecundity (number of offspring) among male patients (5) and female patients (2,6) with schizophrenia. Unfortunately, these studies do not clearly describe the use of psychotropic medications among these patients.

The deinstitutionalization of patients with chronic mental illness was encouraged to a large degree by the development of neuroleptic medications. All such medications developed before the 1980s shared a common characteristic of nonselective dopaminergic blockade, now known to involve the D_2 receptor in particular. Shortly after the introduction of chlorpromazine in 1954, side effects referable to dopaminergic pathways became clear. The antipsychotic effects of these medications were due to their actions in the mesolimbic and mesocortical areas. Movement disorders became manifest due to action in the nigrostriatal areas. Neuroendocrine effects were related to dopaminergic blockade in the tuberoinfundibular system.

These latter effects may be mediated through two routes. First, dopamine inhibits synthesis and release of prolactin in the anterior pituitary. Second, neuroleptics may exert a direct action on the hypothalamic-pituitary axis, which modulates pituitary response irrespective of the activity of prolactin (7). By either or both mechanisms, ovulation is interrupted by disruption of the gonadotrophin-releasing pulse generator system (8,9).

Researchers have attempted to correlate neuroleptic-induced hyperprolactinemia with a variety of clinical and research correlates. However, although prolactin levels may reflect the bioavailability of neuroleptic medication and central nervous system activity (10), a simple linear relationship between prolactin levels and neuroleptic levels or clinical response to antipsychotic medications does not exist. Prolactin is increased eight- to tenfold within one hour of intramuscular administration of haloperidol (11,12). Many studies exclude female research subjects, and more data exist for male subjects. In research that has included both male and female patients, women experienced an increased prolactin surge at lower neuroleptic doses than men (13).

Increased prolactin is associated with a variety of side effects, including weight gain, decreased libido,

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galactorrhea, and amenorrhea. In one study of 29 female patients with schizophrenia treated with thiordazine, 91 percent reported changes in menstruation, and reversible amenorrhea occurred in 50 percent of subjects (14). The effects of long-term neuroleptic use on prolactin levels are the subject of debate. Some researchers have found sustained prolactin elevation with chronic use of neuroleptic medications (15), while others have documented a slow return of prolactin levels toward baseline (12,16). Long-term studies of menstrual patterns are lacking.

More recently, newer antipsychotic medications with fewer effects at the D_2 receptor have been developed. Risperidone exhibits D_2-affinity that is similar to haloperidol, elicits a similar if not greater prolactin response, and therefore should have similar effects on menstruation. However, medications such as clozapine, olanzapine, and other atypical agents demonstrate an entirely different side effect profile. As these medications spare postsynaptic dopamine receptors, there is no elevation of prolactin levels and therefore no secondary amenorrhea (17).

Case reports of pregnancies associated with initiation of clozapine treatment have appeared (1,18). Pregnancy risk was presumed to be associated both with increased fertility and with improved social interaction. However, no controlled studies of fertility rates for women treated with these agents have been reported. Therefore, clinicians treating sexually active patients with both the older and the newer antipsychotic agents should monitor endocrine side effects judiciously.

Although further work remains to be done, evidence to date suggests the possibility of increased fertility among patients taking the newer-line agents. Theoretically, women taking risperidone may be less likely to become pregnant than those taking olanzapine, for example. This difference could argue for the establishment of a case registry to follow these trends.

It is our perception that patients with chronic mental illness often do not have access to routine medical care and that public-sector psychiatrists are increasingly involved in primary medical care for these patients. As part of such care, a comprehensive sexual history should be obtained. Along with discussions of prevention of sexually transmitted diseases, the topic of family planning should be approached. Among other clinical reasons dictating choice of antipsychotic medications, clinicians and patients should be aware of the endocrine effects of the various medications and their potential to cause alterations in fertility. ♦

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