

antipsychotics with less potential to elevate prolactin.<sup>95-98</sup> While these new agents have been used to treat female patients with antipsychotic-induced hyperprolactinemia,<sup>99,100</sup> studies of the relationship between antipsychotic-induced hyperprolactinemia and ovarian function in women with schizophrenia are rather limited.

Although menstrual abnormalities have been cited in up to 50-75% of women treated with antipsychotics,<sup>101-105</sup> these reports do not describe the relationship of such abnormalities to serum prolactin levels. More recent studies designed to examine this relationship have failed to show significant differences in the prolactin levels of female patients with and without menstrual dysfunction.<sup>89,94,106-108</sup> Additionally, even studies of risperidone, which may have the most potential to elevate prolactin,<sup>109,110</sup> found no correlation between treatment-induced hyperprolactinemia and the emergence of prolactin-related side effects, including amenorrhea.<sup>111,112</sup> While one study<sup>113</sup> reported an inverse relationship between prolactin and estrogen levels in female patients with schizophrenia, other studies found no correlation between prolactin and estrogen levels in this patient population.<sup>89,114</sup> Although there does not appear to be a clear relationship between prolactin and estrogen levels in these patients, a number of recent studies,<sup>71,72,89,94,114,115</sup> as well as a carefully conducted study from the pre-neuroleptic era,<sup>116</sup> have suggested that women with schizophrenia do have diminished estrogen levels.

Osteoporosis is associated with both hyperprolactinemia and hypoestrogenism.<sup>117,118</sup> Several authors have suggested that patients with schizophrenia are at increased risk for osteoporosis, due possibly to antipsychotic-induced hyperprolactinemia as well as other associated risk factors such as cigarette smoking, polydipsia, and lack of exercise.<sup>119,120</sup> Since hyperprolactinemic bone loss appears to be related to the duration of prolactin elevation rather than to the absolute levels,<sup>121</sup> it will be important for future research to establish the extent to which antipsychotic-induced hyperprolactinemia, per se, contributes to the risk of osteoporosis in this population requiring chronic treatment.

Galactorrhea, a classic clinical manifestation of hyperprolactinemia, has been reported in 19-50% of female patients treated with antipsychotic medications.<sup>122,123</sup> While galactorrhea is a benign condition, the long-term effect of prolactin elevation on breast tissue is unknown. Although theories of breast cancer development stress the role of estrogen, rather than prolactin, as a risk factor, whether chronic treatment

with antipsychotics increase risk for breast cancer has been a matter of some concern. A study using mammography to compare the incidence of breast cancer in chronic psychiatric patients to patients at a general medical clinic reported a 3.5 times higher incidence of breast cancer in the psychiatric population.<sup>124</sup> Although such findings are concerning, it is not known whether the purported increased cancer rate is related to the use of prolactin-elevating medication. In addition, results from epidemiologic studies are equivocal; the majority of studies show no increased prevalence in breast cancer among antipsychotic-exposed females with schizophrenia,<sup>125-127</sup> or a small increase in females exposed to typical antipsychotics in an uncontrolled sample.<sup>128</sup>

The long-term consequences of antipsychotic-induced hyperprolactinemia are unknown. While there may be differential liability for various antipsychotics to elevate serum prolactin, the risk of hyperprolactinemia must be weighed against the risk of other clinically significant effects such as weight gain and altered glucose and lipid metabolism.<sup>129,130</sup>

## Hypothalamic-Pituitary-Ovarian Manifestations of Schizophrenia

Based on several studies reporting high rates of menstrual dysfunction and/or diminished estrogen levels, irrespective of prolactin levels, we have speculated that ovarian dysfunction may be a neuroendocrine manifestation of schizophrenia in women. Since dopamine plays an important role in regulating the hypothalamic-pituitary-ovarian axis,<sup>131</sup> the dopamine dysregulation thought to underlie psychosis may also impair ovarian function.<sup>89</sup> Further research is necessary to assess whether such ovarian dysfunction is primarily related to the schizophrenic process and whether hormone replacement therapy or selective estrogen receptor modulators might provide clinical benefit to women with the disorder.

## CONCLUSION

The literature suggests that women and men with schizophrenia manifest the illness differently. Women with schizophrenia tend to have better premorbid functioning, a later age and distinct pattern of onset, a more favorable course of illness, different cognitive deficits, and during the premenopausal years, a superior treatment response to typical antipsychotics compared to men. Such differences are thought to arise from an interaction between sex hormones and