Reproductive Hormone Sensitivity and Obsessive-Compulsive Disorder: Are There Differences in the Genetic Predisposition Between Symptom Dimensions?

To the Editor: We have read with interest the recent article by Forray et al,[1] which provides additional evidence that pregnancy and postpartum are associated with the onset of obsessive-compulsive disorder (OCD) and the worsening of symptoms in women with preexisting OCD. The hormone-related vulnerability of some women with OCD was also pointed out by our group. We previously described that subjects with OCD and premenstrual mood symptoms more frequently reported premenstrual worsening of OCD and an onset (or worsening of previous OCD) at postpartum.[2] In addition, we also found that women with a history of premenstrual worsening of OCD more frequently report changes in OCD symptoms while taking oral contraceptive pills.[3]

As Forray et al[1] suggest, genes that regulate reproductive hormone signaling may play a role in this biological predisposition. The estrogen receptor α gene (*ESR1*), which has been linked to premenstrual dysphoric disorder,[4] seems to be a good candidate. In a recent study by our group,[5] we genotyped 29 single-nucleotide polymorphisms (SNPs) in estrogen receptor genes (*ESR1* and *ESR2*) in 229 OCD patients and 279 controls. Although we did not find significant differences in the distribution of alleles or genotypes between controls and OCD subjects, when we analyzed OCD subphenotypes we found that the SNP rs34535804 in *ESR1* and a 5-SNPs haplotype located in the 5′ end of intron 1 of *ESR1* were associated with the presence of contamination obsessions and cleaning compulsions. We observed that carriers of the rs34535804*A-rs488133*C-rs9478245*C-rs2234693*C-rs9340799*G haplotype, a combination of functional alleles related with higher estrogen receptor α expression, showed a reduced risk of suffering from these symptoms. Interestingly, in another study[6] that included 90 women with OCD, we concluded that the onset of the disorder in patients reporting contamination/cleaning symptoms was more frequently related to the perinatal period. In accordance with our study, Forray et al.[1] also found that of all obsessive-compulsive symptoms, only contamination obsessions were significantly greater in the perinatal-related subgroup when compared to the nonperinatal-related subgroup.

OCD is heterogeneous in its clinical manifestations, and patients may show distinct symptom patterns. Obsessions and compulsions are experienced within multiple overlapping symptom dimensions[7]: contamination/cleaning, aggressive/checking, symmetry/ordering, and hoarding. These dimensions are also mediated by different components of the frontostriatal-thalamic circuits involved in cognitive and emotion processing,[8] and may differ in their genetic risk.[9] The recent study by Alonso et al,[5] together with the clinical information regarding the positive relationship between contamination/cleaning symptoms and the perinatal onset of OCD,[1,6] suggests that women

© Copyright 2011 Physicians Postgraduate Press, Inc.

with symptoms from the cleaning dimension may carry a genetic vulnerability that could make them more susceptible to fluctuations in gonadal steroids. Future studies need to assess whether this vulnerability to reproductive events is driven by a different genetic risk (eg, *ESR1* gene), as we hypothesize. Moreover, these studies should control for the phenotype, as the biological risk for being susceptible to changes in gonadal steroids may be greater for women with contamination obsessions or cleaning compulsions.

References

1. Forray A, Focseneanu M, Pittman B, et al. Onset and exacerbation of obsessive-compulsive disorder in pregnancy and the postpartum period. *J Clin Psychiatry*. 2010;71(8):1061–1068.
2. Labad J, Menchón JM, Alonso P, et al. Female reproductive cycle and obsessive-compulsive disorder. *J Clin Psychiatry*. 2005;66(4):428–435, quiz 546.
3. Labad J, Menchón JM, Alonso P, et al. Oral contraceptive pill use and changes in obsessive-compulsive symptoms. *J Psychosom Res*. 2006;60(6):647–648.
4. Huo L, Straub RE, Roca C, et al. Risk for premenstrual dysphoric disorder is associated with genetic variation in ESR1, the estrogen receptor alpha gene. *Biol Psychiatry*. 2007;62(8):925–933.
5. Alonso P, Gratacòs M, Segalàs C, et al. Variants in estrogen receptor alpha gene are associated with phenotypical expression of obsessive-compulsive disorder. *Psychoneuroendocrinology*. 2010; In press.
6. Labad J, Alonso P, Segalàs C, et al. Distinct correlates of hoarding and cleaning symptom dimensions in relation to onset of obsessive-compulsive disorder at menarche or the perinatal period. *Arch Women Ment Health*. 2010;13(1):75–81.
7. Bloch MH, Landeros-Weisenberger A, Rosario MC, et al. Meta-analysis of the symptom structure of obsessive-compulsive disorder. *Am J Psychiatry*. 2008;165(12):1532–1542.
8. Mataix-Cols D, Wooderson S, Lawrence N, et al. Distinct neural correlates of washing, checking, and hoarding symptom dimensions in obsessive-compulsive disorder. *Arch Gen Psychiatry*. 2004;61(6):564–576.
9. Hasler G, Pinto A, Greenberg BD, et al; OCD Collaborative Genetics Study. Familiality of factor analysis-derived YBOCS dimensions in OCD-affected sibling pairs from the OCD Collaborative Genetics Study. *Biol Psychiatry*. 2007;61(5):617–625.

Javier Labad, MD
labadj@peremata.com
Pino Alonso, MD, PhD
Cinto Segalàs, MD
Eva Real, MD
José Manuel Menchón, MD, PhD

Author affiliations: Hospital Psiquiàtric Universitari Institut Pere Mata, IISPV, Universitat Rovira i Virgili, Reus (Dr Labad); OCD Clinical and Research Unit, Department of Psychiatry, Bellvitge University Hospital, L'Hospitalet de Llobregat, Barcelona (Drs Alonso, Segalàs, Real, and Menchón); Department of Clinical Sciences, Bellvitge Campus, University of Barcelona, Barcelona and CIBERSAM (Centro de Investigación en Red de Salud Mental), Instituto de Salud Carlos III (Drs Alonso and Menchón); and Institut d' Investigació Biomèdica de Bellvitge (IDIBELL), L'Hospitalet de Llobregat, Barcelona (Dr Real), Spain.

Potential conflicts of interest: None reported. ***Funding/support:*** Dr Menchón received grants from the Instituto de Salud Carlos III (FIS PI071044) and CIBERSAM (CIBER-CB06/03/0034). Dr Alonso received a grant from the Instituto de Salud Carlos III (FIS PI071029).
doi:10.4088/JCP.10l06481blu