

Possible Relation of Antenatal Venlafaxine Use and VACTERL Association in a Newborn: A Case Report



Muammer Özgür ÇEVİK¹, Mustafa ÇELİK², İbrahim Hakan BUCAK³, Behice HAN ALMİS⁴,
Mehmet TURĞUT⁵

SUMMARY

Major depressive disorder is common during the antenatal period and many women are prescribed antidepressant drugs although antidepressants have not been definitively regarded as safe in pregnancy. Previous studies have suggested a link between gestational use of selective serotonin reuptake inhibitors (SSRI) or serotonin and norepinephrine reuptake inhibitors (SNRI) and certain birth defects.

VACTERL association is a rare group of congenital malformations which were observed to occur together more often than would be expected by chance. Diagnosis requires coexistence of at least three congenital malformations from the vertebral (V), anal (A), cardiac (C), tracheoesophageal (TE), renal (R), and limb (L) regions.

Here, we report a case of a newborn female whose mother's gestational history revealed venlafaxine use before and during her pregnancy. This newborn had anal atresia, patent ductus arteriosus, tracheoesophageal fistula, and upper limb anomalies.

To the best of the authors' knowledge, this is the first report of VACTERL association possibly related to gestational use of an SSRI or SNRI.

Keywords: Venlafaxine, VACTERL association, Congenital Abnormalities

INTRODUCTION

The risk of depression recurrence in previously depressed women is high during the perinatal period (Marcus et al. 2003, Andersson et al. 2003). Although no antidepressants have obtained approval from boards such as United States Food and Drug Agency (FDA) for use during pregnancy and/or lactation periods, many pregnant women use prescribed or non-prescribed antidepressant drugs. A study in Canada which compared outcomes of pregnancies of 1243 women who used antidepressants during pregnancy with 1243 women who did not use antidepressants could not find an association between the antenatal use of antidepressants including venlafaxine and congenital malformations in newborns

(Einarson et al. 2009). However, some studies yield conflicting results. Louik et al (2007) investigated 9849 newborns with and 5860 newborns without congenital malformations. They were unable to find an association between the use of selective serotonin reuptake inhibitors (SSRIs) during pregnancy and congenital malformations but they found associations between sertraline use and omphalocele or septal defects and between paroxetine use and right ventricular outflow tract obstruction. Alwan et al. (2007) evaluated 9622 newborns with and 4092 newborns without congenital malformations. They could not find an association between SSRI use during pregnancy and congenital malformations in general; but, the rate of anencephaly, craniosynostosis and omphalocele were

Received: 23.02.2015 - Accepted: 22.05.2015

¹Assist. Prof., Adiyaman University, Genetics Department, ²Assist. Prof., Adiyaman University, Psychiatry Department, ³Assist. Prof., ⁴Assist. Prof., ⁵Prof., Adiyaman University, Pediatrics Department, Adiyaman, Turkey.

e-mail: mustacelik@yahoo.com

doi: 10.5080/u13515

significantly higher in newborns whose mothers used SSRIs during pregnancy.

Venlafaxine is a serotonin and norepinephrine reuptake inhibitor (SNRI) antidepressant. Its pregnancy category is C which is defined as “animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks” (FDA, 1979). Few studies have examined the teratogenic potential of venlafaxine use during pregnancy. Einarson et al. (2001) compared the outcomes of 150 women who used venlafaxine during pregnancy with 150 women who used SSRIs and 150 women who used drugs known to be non-teratogenic. They were unable to find a congenital malformation that increased significantly in the venlafaxine group. On the other hand, Polen et al. (2013) investigated data from the National Birth Defects Prevention Study (NBPDS) and found that the incidences of anencephaly, atrial septal defect (ASD), aortic coarctation, cleft palate, and gastroschisis significantly increased in newborns of women exposed to venlafaxine during pregnancy.

VACTERL association is defined as the presence of at least 3 congenital anomalies of the vertebral (V), anal (A), cardiac (C), tracheoesophageal (TE), renal (R), and limb (L) regions (Rittler et al. 1996). This condition was first named as VATER association and was defined as the presence of a group of congenital anomalies including vertebral defects, anal atresia, tracheoesophageal fistulae or esophageal atrophy, and radial and renal dysplasia occurring together more often than expected by chance statistically (Quan and Smith 1973). This condition was defined as an association because the anomalies are observed more frequently than they can be observed together by chance and it was not named as a syndrome because a common underlying mechanism had yet to be explained (Solomon 2011). Our literature search revealed only one case of VACTERL/VATER association due to antenatal use of antidepressants and in that case the mother used a tricyclic drug, dibenzepin (Merlob and Naor 1994). To the best of our knowledge, VACTERL association related with antenatal venlafaxine use has never been reported before. We present the case of a baby girl diagnosed with VACTERL association whose mother used venlafaxine before and during her pregnancy.

CASE

A newborn baby girl was consulted to the pediatrics department for evaluation of ventriculomegaly which was detected at prenatal ultrasound. Her father was 40 and mother was 30 years old and they were 3rd degree relatives. The mother did not have diabetes, or obesity (BMI of 23.4) and she denied the use of fertility treatments, alcohol or illegal drugs,



Figure 1: Bilateral oligodactyly at hands (thumbs are absent) and forearm anomaly.



Figure 2: Anal atresia



Figure 3: Esophagus atresia detected by barium X-ray

or smoking during pregnancy. She was the third child of the family after two healthy siblings. The mother was evaluated 3 months before this pregnancy by a psychiatrist with complaints of depressed mood, anhedonia, inability to sleep, and anorexia. With a diagnosis of major depressive disorder, venlafaxine 75 mg/day was started. She did not go to control visits but she continued to use venlafaxine during her pregnancy because she felt well with the medication. She visited the obstetrics and gynecology clinic 4 times during her pregnancy but she did not mention her venlafaxine usage. Intrauterine growth retardation was detected at the prenatal ultrasound.

The child was born at the 38th week of gestation but the prenatal ultrasound was consistent with the 32nd week. The APGAR score was 5 at the 1st minute and 7 at the 5th minute after birth. Her birth weight was 1880g (<3 percentile), height was 46 cm (3-10 percentile) and head circumference was 32 cm (3-10 percentile). Physical examination revealed oligodactyly (no thumb), bilateral absence of the ulnas, and bilateral shortness of the radii (Figure 1). In addition anal atresia and rectovaginal fistula were detected by inspection (Figure 2).

We tried to place a nasogastric tube but were not able to do so. Thus, we requested a barium X-ray and detected esophageal atrophy and tracheoesophageal fistula (Figure 3). Her karyotype analysis revealed a 46, XX female. G band staining revealed no structural or numerical chromosomal defect.

Cardiac auscultation revealed a continuous systolic murmur, and echocardiography demonstrated a patent ductus arteriosus (PDA; 4 mm) and moderate (10-20 mm) pericardial effusion. No intervention was attempted because her general condition was poor. She died after cardiopulmonary arrest a week after her hospitalization.

DISCUSSION

To diagnose VACTERL association, at least 3 anomalies should be found at defined areas (vertebral, anal, cardiac, tracheoesophageal, renal and extremities) (Solomon et al. 2011, Shaw-Smith 2010). Our patient had bilateral oligodactyly and ulnar agenesis, anal atresia and rectovaginal fistula, esophageal agenesis and tracheoesophageal fistula, and a PDA. With anomalies at 4 areas we diagnosed VACTERL association.

The differential diagnosis included the evaluation of rare syndromes. We excluded Alagille syndrome (no characteristic facial appearance or ophthalmic anomalies), Baller-Gerold syndrome (no skin anomalies or craniosynostosis), CHARGE syndrome (no coloboma, ear anomalies or facial features), Currarino syndrome (no presacral mass), 22q11.2 deletion syndrome (karyotyping was normal), Fanconi's anemia (no abnormalities in pigmentation or hematologic parameters), Feingold's syndrome (no syndactyly at toes), Fryns' syndrome (no diaphragmatic abnormality or facial anomalies), MURCS

association (no syndactyly), oculo-auriculo-vertebral syndrome (no microtia or hemifacial microsomia), Opitz G/BBB syndrome (no syndactyly or hypertelorism, Pallister-Hall syndrome (no nail hypoplasia or bifid epiglottis), and Townes-Brocks syndrome.

The etiology of VACTERL association is unknown and many cases occur sporadically (Solomon 2011). Several authors have tried to explain the occurrence of multiple anomalies at multiple organ systems and have suggested the concept of a developmental field defect (Opitz 1985). According to this hypothesis, problems during blastogenesis may impair cellular migration and this causes congenital malformations affecting multiple organ systems (Martinez-Frias et al. 1998). A small percentage of VACTERL cases show familial clustering and this suggests hereditary factors may also play role (Brown et al. 1999). Moreover, environmental factors such as diabetes mellitus and infertility treatments of mothers (intrauterine exposure to estrogen and/or progesterone) are reported to increase the risk of VACTERL association (Nora and Nora 1975, Castori et al. 2008). In some patients, features defining VACTERL association were seen due to mitochondrial functional impairment (Damian et al. 1996), chromosomal deletion or duplication like in trisomy 18 (van der Veken et al. 2010), and mutations in HOXD13 (Zhao et al. 2007) and ZIC3 (Gebbia et al. 1997) genes. In our case we excluded maternal diabetes and intrauterine exposure to progesterone and/or estrogen by maternal medical history and also excluded chromosomal deletions/duplications by karyotype analysis. In addition, she did not have a relative with a congenital anomaly.

The sonic hedgehog (SHH) signaling pathway appears to be a plausible candidate to explain potential teratogenic effects of antidepressants including venlafaxine. For example, the HOXD13 gene, whose mutations cause features of VACTERL association is included in the SHH signal pathway (Agochukwu et al. 2011). SHH gene expression is reported to be regulated by nuclear factor kappa B (NFκB) light chains of activated B cells (Kasperczyk et al. 2009). Also, NFκB is regulated by TNFα (Fitzgerald et al. 2007). Studies that have evaluated the teratogenic effects of TNFα inhibitors supported the role of TNFα in the pathogenesis of VACTERL association. Carter et al. (2009) searched data of women exposed to TNFα inhibitors during pregnancy from an FDA database and found that components of VACTERL association were seen significantly more frequently in newborns of these women. Venlafaxine was found to inhibit TNFα increase (Li et al. 2013). According to this data, the link between prenatal exposure to venlafaxine and VACTERL association may involve TNFα, NFκB, and the SHH signaling pathway.

Of course, a case report is not adequate to explain the cause-effect relationship and in this case venlafaxine use and VACTERL association might have been coincidental.

Nevertheless, physicians should be cautious about the use of antidepressants in mothers of newborns with anomalies involving components of the VACTERL association. Because the incidence of VACTERL association is so low, components of this association may be studied to draw statistically significant results.

While evaluating risks of antidepressant use during pregnancy potential hazards of untreated depression on the fetus should also be considered. Previous studies have found associations between untreated depression during pregnancy and increased rate of stillbirths (Michel-Wolffromm 1968), low Apgar scores (Zax et al. 1977), low birthweight in infants (Preti et al. 2000), birth complications (Paarlberg et al. 1995), and premature birth (Chung et al. 2001). Antidepressant use in pregnancy is an important concern both because the aforementioned risks of not using antidepressants necessitate antidepressant use in many pregnant women and because many pregnant women inadvertently continue antidepressants which were started before pregnancy. To decrease risks of antidepressant use during pregnancy, caution should be exercised when prescribing antidepressants to pregnant women, patients should be informed about the potential effects of antidepressants during pregnancy, and pregnant women with a history of antidepressant use during the first trimester should be followed closely and meticulously.

REFERENCES

- Agochukwu NB, Pineda-Alvarez DE, Keaton AA et al (2011) Analysis of FOXF1 and the FOX gene cluster in patients with VACTERL association. *Eur J Med Genet* 54:323-8
- Alwan S, Reefhuis J, Rasmussen SA et al (2007) National Birth Defects Prevention Study. Use of selective serotonin-reuptake inhibitors in pregnancy and the risk of birth defects. *N Engl J Med* 356:2684-92
- Andersson L, Sundström-Poromaa I, Bixo M et al (2003) Point prevalence of psychiatric disorders during the second trimester of pregnancy: a population-based study. *Am J Obstet Gynecol* 189:148-54.
- Brown AK, Roddam AW, Spitz L et al (1999) Oesophageal atresia, related malformations, and medical problems: a family study. *Am J Med Genet* 85:31-7
- Carter JD, Ladhani A, Ricca LR et al (2009) A safety assessment of tumor necrosis factor antagonists during pregnancy: a review of the Food and Drug Administration database. *J Rheumatol* 36:635-41
- Castori M, Rinaldi R, Capocaccia P et al (2008) VACTERL association and maternal diabetes: a possible causal relationship? *Birth Defects Res A Clin Mol Teratol* 82:169-72
- Chung TK, Lau TK, Yip AS et al (2001) Antepartum depressive symptomatology is associated with adverse obstetric and neonatal outcomes. *Psychosom Med* 63:830-4.
- Daman MS, Seibel P, Schachenmayr W et al (1996) VACTERL with the mitochondrial np 3243 point mutation. *Am J Med Genet* 62:398-403
- Einarson A, Choi J, Einarson TR et al (2009) Incidence of major malformations in infants following antidepressant exposure in pregnancy: results of a large prospective cohort study. *Can J Psychiatry* 54:242-6.
- Einarson A, Fatoye B, Sarkar M et al (2001) Pregnancy outcome following gestational exposure to venlafaxine: a multicenter prospective controlled study. *Am J Psychiatry* 158:1728-30.
- Fitzgerald DC, Meade KG, McEvoy AN et al (2007) Tumour necrosis factor- α (TNF- α) increases nuclear factor kappaB (NF-kappaB) activity in and interleukin-8 (IL-8) release from bovine mammary epithelial cells. *Vet Immunol Immunopathol* 116: 59-68
- Gebbia M, Ferrero GB, Pilia G et al (1997) X-linked situs abnormalities result from mutations in ZIC3. *Nat Genet* 17:305-8
- Kasperczyk H, Baumann B, Debatin KM et al (2009) Characterization of sonic hedgehog as a novel NF-kappaB target gene that promotes NF-kappaB-mediated apoptosis resistance and tumor growth in vivo. *FASEB J* 23:21-33
- Li Z, Qi D, Chen J et al (2013) Venlafaxine inhibits the upregulation of plasma tumor necrosis factor- α (TNF- α) in the Chinese patients with major depressive disorder: a prospective longitudinal study. *Psychoneuroendocrinology* 38:107-14
- Louik C, Lin AE, Werler MM et al (2007) First-trimester use of selective serotonin-reuptake inhibitors and the risk of birth defects. *N Engl J Med* 356:2675-83.
- Marcus SM, Flynn HA, Blow FC et al (2003) Depressive symptoms among pregnant women screened in obstetrics settings. *J Womens Health Care* 12:373-80.
- Martínez-Frías ML, Frías JL, Opitz JM (1998) Errors of morphogenesis and developmental field theory. *Am J Med Genet* 76:291-6
- Merlob P, Naor N (1994) Drug induced VATER association: is dibenzepin a possible cause? *J Med Genet* 31:423-7
- Michel-Wolffromm H (1968) The psychological factor in spontaneous abortion. *J Psychosom Res* 12:67-71.
- Nora AH, Nora JJ (1975) A syndrome of multiple congenital anomalies associated with teratogenic exposure. *Arch Environ Health* 30:17-21.
- Opitz JM (1985) The developmental field concept. *Am J Med Genet* 21:1-11
- Paarlberg KM, Vingerhoets AJ, Passchier J et al (1995) Psychosocial factors and pregnancy outcome: a review with emphasis on methodological issues. *J Psychosom Res* 39:563-95
- Polen KN, Rasmussen SA, Riehle-Colarusso T et al (2013) National Birth Defects Prevention Study. Association between reported venlafaxine use in early pregnancy and birth defects, national birth defects prevention study, 1997-2007. *Birth Defects Res A Clin Mol Teratol* 97:28-35
- Preti A, Cardascia L, Zen T et al (2000) Obstetric complications in patients with depression—a population-based case-control study. *J Affect Disord* 61:101-6.
- Quan L, Smith DW (1973) The VATER association. Vertebral defects, Anal atresia, T-E fistula with esophageal atresia, Radial and Renal dysplasia: a spectrum of associated defects. *J Pediatr* 82:104-7.
- Rittler M, Paz JE, Castilla EE (1996) VACTERL association, epidemiologic definition and delineation. *Am J Med Genet* 63:529-6
- Shaw-Smith, C (2010) Genetic factors in esophageal atresia, tracheo-esophageal fistula and the VACTERL association: Roles for FOXF1 and the 16q24.1 FOX transcription factor gene cluster, and review of the literature. *Eur J Med Genet* 53: 6-13.
- Solomon BD (2011) VACTERL/VATER Association. *Orphanet J Rare Dis* 6:56
- Solomon, BD, Raam, MS, Pineda-Alvarez, DE (2011) Analysis of genitourinary anomalies in patients with VACTERL (Vertebral anomalies, Anal atresia, Cardiac malformations, Tracheo- Esophageal fistula, Renal anomalies, Limb abnormalities) association. *Congenit Anom (Kyoto)* 51, 87-91.
- US Food and Drug Administration. 1979. Labeling and prescription drug advertising: Content and format for labeling for human prescription drugs. *Federal Register* 44:37434-67.
- van der Veken LT, Dieleman MM, Douben H et al (2010) Low grade mosaicism for a complex supernumerary ring chromosome 18 in an adult patient with multiple congenital anomalies. *Mol Cytogenet* 3:13
- Zax M, Sameroff AJ, Babigian HM (1977) Birth outcomes in the offspring of mentally disordered women. *Am J Orthopsychiatry* 47:218-30.
- Zhao X, Sun M, Zhao J et al (2007) Mutations in HOXD13 underlie syndactyly type V and a novel brachydactyly-syndactyly syndrome. *Am J Hum Genet* 80:361-71