DSJUOG

10.5005/jp-journals-10009-1345

LIFELONG LEARNING

# Psychotropic Medication Use during Pregnancy and Lactation: Role of Ultrasound Assessment

[1]Andrew Matthys, [2]Maria Teresa Ambat, [3]Ritsuko Pooh, [4]Sanja Kupesic Plavsic

## ABSTRACT

The potential teratogenic effects of psychotropic medication use during pregnancy have been scrutinized ever since thalidomide contributed to phocomelia in the 1950's. Up to 35% of the half a million women becoming pregnant each day take psychotropic medication(s). Teratogens alter normal intrauterine fetal growth, anatomic structures, functioning and postnatal development. In this educational review article, we examine whether different classes of psychotropic medications have the potential to be teratogens or have other nonteratogenic effects. Specifically, we examined antidepressants (SSRIs, TCAs), anticonvulsants (valproate, carbamazepime, lamotrigine), antipsychotics, Benadryl and Lithium. We also provided case reports with ultrasound images as well as a review quiz.

**Keywords:** Psychotropic medication, Pregnancy, Birth defects, Teratogens, Ebstein's anomaly, Withdrawal, SSRIs, TCAs, Anticonvulsants, Valproate, Valproic acid, Carbamazepine, Lamotrigine, Antipsychotics, Haloperidol, Olanzapine, Benadryl, Lithium.

**How to cite this article:** Matthys A, Ambat MT, Pooh R, Kupesic Plavsic S. Psychotropic Medication Use during Pregnancy and Lactation: Role of Ultrasound Assessment. Donald School J Ultrasound Obstet Gynecol 2014;8(1):109-121.

**Source of support:** Nil

**Conflict of interest:** None

## INTRODUCTION

Ever since the congenital birth abnormality, phocomelia, was attributed to thalidomide use during pregnancy in the late 1950's, there has been increasing scrutiny on the use of psychotropic medication during pregnancy. With more than half a million women in the world getting pregnant each day and a growing prevalence of psychotropic medication use among women of childbearing age, the concern over the effects of these medications on fetal development is well founded.[1] Studies have indicated that between 50 and 80% of women have taken prescription drugs during their pregnancy and up to 35% of these women used psychotropic medication (including antidepressants, anxiolytics, antipsychotics and mood stabilizers).[2,3] The major concern with using these medications during pregnancy is the risk of causing future harm to the unborn infant, with many of these medications being linked to adverse pregnancy outcomes, such as teratogenesis or spontaneous abortions.[4-79] Teratogens are factors, including drugs, environmental exposures, maternal medical conditions, genetic causes and infectious agents, which can alter normal intrauterine fetal growth, anatomic structures, functioning and postnatal development.[5-7] The most fragile period for the developing embryo is between 2 and 8 weeks since it is a critical period of organ formation. After this critical developmental window, teratogenic drugs rarely produce gross structural malformations but can affect the growth and functional development of other fetus' organs, especially the central nervous system, leading to motor and cognitive delay. There can also be nonteratogenic adverse effects on the newborn, such as withdrawal from the medication after delivery. However, an untreated psychiatric illness in a pregnant woman can be disastrous for the mother and for the fetus. Untreated psychiatric illness in the pregnant women could lead to poor compliance with prenatal care; use of illicit drugs, alcohol or cigarettes to self-medicate; poor nutrition; relationship problems with the mother and her support system as well as maternal suffering and disruption in maternal-infant bonding postpartum. Overall, it has been suggested that psychotropic drugs be used in pregnancy only when the risk to the mother and fetus of not using medications outweighs the risk of drug treatment. Most psychotropic medication should be avoided in the first trimester, if possible. If treatment is necessary, use the lowest effective dose and use monotherapy whenever possible. If discontinuing the medication, the pregnant women should be advised to taper the medication dose down. The main effects of each class of psychotropic medication are listed in Table 1.

[1]Student Physician, [2]Assistant Professor, [3]Professor, [4]Assistant Dean and Professor

[1,4]Department of Obstetrics and Gynecology, Paul L Foster School of Medicine, Texas Tech University Health Sciences Center at El Paso, Texas, USA

[2]Department of Pediatrics, Paul L Foster School of Medicine Texas Tech University Health Sciences Center at El Paso Texas, USA

[3]CRIFM Clinical Research Institute of Fetal Medicine, Tennoji Osaka, Japan

**Corresponding Author:** Sanja Kupesic Plavsic, Assistant Academic Dean for Faculty Development, Professor Department of Obstetrics and Gynecology, Clinical Professor of Radiology, Paul L Foster School of Medicine, Texas Tech University, 4800 Alberta Ave, El Paso, TX 79905, USA Phone: +1 (915)2156505, e-mail: sanja.kupesic@ttuhsc.edu

**Table 1:** The effect of psychotropic medications used in pregnancy and/or lactation

| *Psych Illness: Psychotropic medication* | *Effects in pregnancy and/or lactation* |
|---|---|
| Depression: Antidepressants (SSRIs, TCAs, SNRIs) | • Antidepressants (including SSRIs- sertraline, fluoxetine; TCAs- amitriptyline, nortriptyline; SNRI's- venlafaxine) used during the first trimester have not shown an increased risk of major malformation in the newborn. However, there is controversy over whether there is a very low risk of fetal effects such as miscarriage, stillbirth, preterm birth, shorter gestation and low-birth weight.[33-36] There is no indication to stop tricyclics or SSRIs in early pregnancy.<br>• For newly pregnant patients who have never been on antidepressants with mild to moderate depression, it is suggested that cognitive behavioral therapy or interpersonal psychotherapy be tried first (Grade 2C).[61]<br>• The decision to medicate is based on the severity and frequency of the depressive episode(s), as well as the response to medications in the past. For women with moderate to severe depression and/or a women with a good response to antidepressants in the past, 1st line treatment is antidepressant medication (Grade 2C).[61] Fluoxetine is the best studied SSRI for its safety and efficacy in pregnancy and lactation.<br>• Paroxetine has been associated with congenital heart defects in several studies.[72-74]<br>• Neonates exposed to antidepressants during the second and third trimester should be monitored for withdrawal symptoms after delivery, such as neonatal agitation, infantile colic, drowsiness, dyspepsia, increased startle response, jitteriness, sleeplessness, and seizures. Late 2nd and 3rd trimester exposure to SSRIs (fluoxetine, paroxetine and sertraline) have been associated with a possible increased risk of persistent pulmonary hypertension of the newborn, although more studies need to be performed.[62]<br>• The most important goals in treatment are to maintain a euthymic mood during pregnancy and to prevent significant relapse of depression postpartum. |
| Bipolar disorder: lithium | • For a pregnant bipolar patient with manic, hypomanic, or mixed episodes, the suggested 1st line therapy is 1st generation antipsychotics (haloperidol, fluphenazine). If refractory, then the order of drug preference is risperidone, quetiapine and olanzapine. If still refractive to these therapies, then the last line therapies are lithium, electroconvulsive therapy or lithium + an antipsychotic.<br>• Lithium has been linked to an increased incidence of congenital cardiovascular anomalies including Ebstein's anomaly, especially when taken during the first trimester.[14] (See further details on Ebstein's anomaly on the case reports below).<br>• It is suggested that prenatal screening for anomalies using high-resolution ultrasound occur at 16 to 18 weeks for pregnant women on lithium. Depending on the results of the ultrasound, echocardiography screening should be performed before 20 weeks gestation.[11]<br>• Lithium has also shown to cause fetal toxicity presenting as hypotonia, lethargy, poor reflexes, cardiac arrhythmias and difficulties in respiration.[16]<br>• Newborn infants of women treated with lithium later in pregnancy face potential risks of neonatal toxicity, thyroid and renal dysfunction (including nephrogenic diabetes insipidus).<br>• Serum lithium concentrations should be checked every 2 to 4 weeks during pregnancy, until 36 weeks gestation, at which point levels should be checked weekly.[63]<br>• The risks of lithium to the fetus and the effects of lithium withdrawal on the mother should be discussed before pregnancy.<br>• Women should avoid breastfeeding while taking lithium, since lithium is excreted in the breast milk at 40% of maternal serum levels, which can lead to lithium toxicity in the breastfeeding infant.[37,38] |
| Bipolar disorder: anticonvulsants (valproic acid, carbamazepine, lamotrigine) | • For bipolar patients with major depression, the first line treatment is lamotrigine in adjunct with psychotherapy (Grade 2C). For patients who do not respond or tolerate lamotrigine, it is suggested that quetiapine be used. If refractory to these medications, the suggested therapy is fluoxetine + olanzapine, lamotrigine + lithium or ECT.<br>• Several of the anticonvulsants are folate antagonists, thus leading to a higher risk of neural tube defects (myelocele, meningomyelocele, spina bifida and anencephaly). Therefore, all women on anticonvulsants should receive extra folate (4 mg/day).<br>• Valproic acid carries a high-risk of congenital malformations, such as limb defects, especially in doses over 1000 mg/day during the first trimester.[34]<br>• A fetal valproate syndrome consists of cardiovascular, craniofacial, urogenital, digital and respiratory tract abnormalities.[29-31] It is recommended to avoid valproate as a mood stabilizer in pregnancy.<br>• Studies have shown that exposure to anticonvulsant drugs (esp. valproate) *in utero* may also increase the risk of developing impaired cognitive and motor development, including autism spectrum disorder, later in life.[71]<br>• Studies on lamotrigine have been mixed. Most studies indicate that lamotrigine has no baseline increase in congenital malformations compared with the general population.[66,67] However, other studies show an increase in orofacial clefts.[66]<br>• Carbamazepine has been associated with spina bifida.[77] However, other studies show that carbamazepine is associated with the lowest rate of congenital malformations of all the anticonvulsants.[76]<br>• Valproate is excreted at 1 to 2% of maternal serum levels during lactation and no clinical adverse effects have been noted on the feeding infant. |

*Contd...*

*Contd...*

| | |
|---|---|
| Anxiety: benzodiazepines | • Benzodiazepines have been linked to an increased incidence of cleft palate in infants of mothers who took benzodiazepines during the first trimester.[39] Benzodiazepines should therefore be avoided during the first trimester.<br>• In the second and third trimester, chronic maternal benzodiazepine use may predispose the neonate to toxicity and withdrawal symptoms, leading to floppy baby syndrome.[20] This can present as hypotonia, lethargy, sucking difficulty feeble cry, hypothermia and sometimes, low APGAR score and respiratory depression.<br>• In the largest prospective study, benzodiazepine use in pregnancy was not linked to adverse neurobehavioral development in the exposed children.[70]<br>• Diazepam has been noted to have high milk to plasma ratio. Therefore, it should be avoided during breastfeeding and shorter-acting Lorazepam may be used instead.[6] |
| Schizophrenia: antipsychotics | • Most studies show that prenatal exposure to first- and second- generation antipsychotics do not increase the risk of congenital malformations compared to the general population.[67]<br>• However, chronic administration of antipsychotic medications during the third trimester has been shown to lead to neonatal toxicity and withdrawal symptoms, such as abnormal and increase movements, hyperreflexia, sedation, irritability, difficulty breathing and difficulty feeding.[68]<br>• Studies of antiparkinsonian drugs that are used to treat extrapyramidal symptoms secondary to antipsychotics suggest that organ malformation appears to be less likely with diphenhydramine than amantadine, benztropine or trihexyphenidyl.[69] |

## CASE REPORTS

### Case 1

A 28-year-old (G3P0020) female presents to the clinic for routine follow-up prenatal visit at 16 weeks of gestation. Onset of menarche was at 14 years of age, and age of first intercourse was 19 years old, with no history of sexually transmitted disease. She has a past medical history of long-term major depressive disorder for 5 years, with no suicidal ideation. Her current medications are 40 mg tablets of Fluoxetine for major depression, NSAIDs for chronic pain, and prenatal vitamins. There is no history of familial congenital anomalies. Her history is significant for two spontaneous abortions 2 and 3 years ago. Her ultrasound finding is demonstrated in Figure 1. She questions whether this has been caused by the medication she is on for her major depressive disorder.

### Case 2

A 3-month-old Hispanic male infant was brought to the local community clinic due to difficulty with breastfeeding and constant regurgitation through the nose and the mouth after bottle-feeding. The boy was born term after an uneventful delivery to a 26-year-old woman (G1P1) in Juarez, Mexico, with limited prenatal and postnatal care. Birth weight was 7.5 lbs, which plotted at 50th percentile, with head circumference and birth length at 45th percentile. The mother denied history of hypertension, diabetes or exposure to infectious or radiographic agents during the pregnancy. However, the mother does have a history of anxiety throughout the pregnancy, primarily because of worries about how she is going to have enough money to take care of her new baby. The mother subsequently admitted to self-medicating by going to the local pharmacy and purchasing diazepam, which she used anytime she had severe anxiety or had trouble sleeping. There is no family history of congenital cleft lips or palates in the family and the infant has not received any surgical treatment.

Physical exam revealed a right complete unilateral cleft lip measuring 1 cm in depth and a cleft palate measuring 0.5 cm in depth. The boy is now below the 20th percentile for weight and below the 25th percentile for height given his age. Ultrasound taken during the second trimester can be seen on Figure 2. The rest of the physical exam was normal.

### Case 3

A 23-year-old (G2P1001) female presents to the clinic for a routine follow-up prenatal visit. Her last normal menstrual period was 34 weeks ago. Onset of menarche was 13 years of age, and age of first intercourse was 19 years old with no history of sexually transmitted disease. Her medications include benzoyl peroxide, valproic acid and over the counter Tylenol. Her past medical history includes bipolar disorder type 1, where at the time of her follow-up she was experiencing a manic episode offset by her pregnancy. There is no history of familial congenital anomalies. She had a normal spontaneous vaginal delivery 1 year ago. The prenatal ultrasound revealed a unilateral forearm defect as shown in Figures 3A and B.

On physical exam, her vital signs are: blood pressure 121/80 mm Hg, pulse 115 beats per minute, respiratory rate 22 breaths per minute and temperature is 37°C (98.6°F).

### Case 4

A 21-year-old (G1P0) female presents to the clinic for a routine follow-up prenatal visit at 13 weeks gestation. Onset of menarche was 12 years of age, and age of first

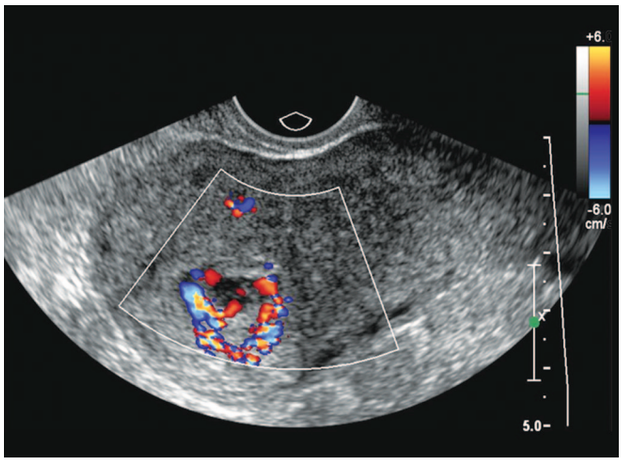
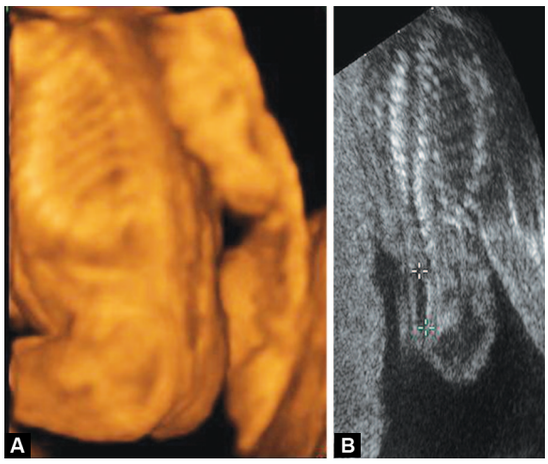



**Fig. 1:** Color Doppler ultrasound of the uterus. Heterogenous material with abundant vascularity is clearly seen in the uterine cavity




**Figs 4A and B:** 3D ultrasound (A, left) and 2D ultrasound (B, right) of the fetal spine

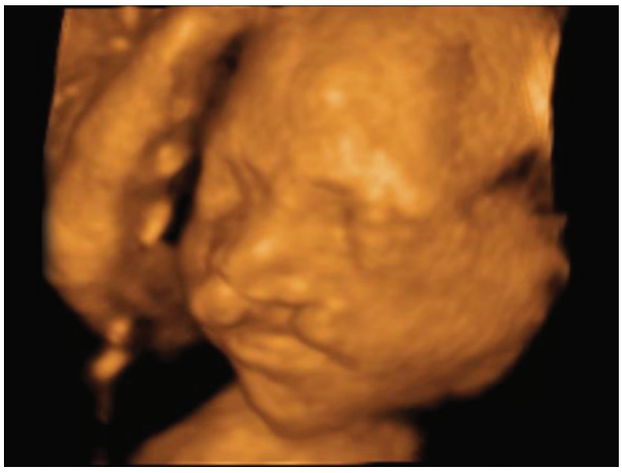
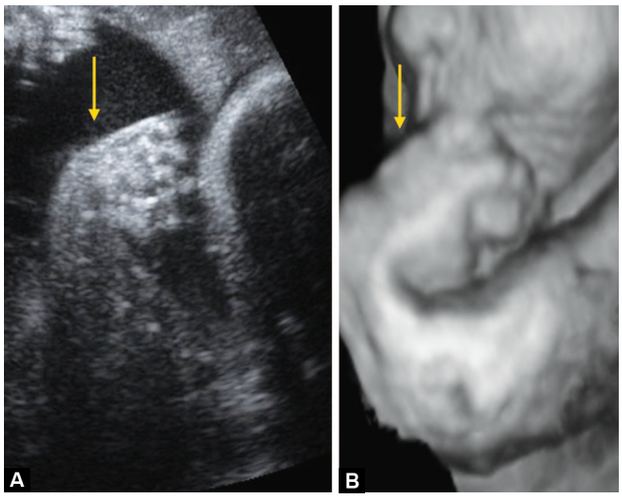


**Fig. 2:** 3D ultrasound image (surface rendering) of the fetal face




**Figs 3A and B:** 2D ultrasound imaging of fetal radius (A, left) and 3D ultrasound corresponding image (B, right)

intercourse was 18 years old with no history of sexually transmitted disease. She has a past medical history of bipolar disorder type 1 that is treated with valproic acid. She is on no other current medication and denies taking any folic acid supplements. Her father was also diagnosed with bipolar disorder type 2 and her mother has hypertension and diabetes type 2, but there is no family history of congenital anomalies. Laboratory results show an α-fetoprotein level of 2.5 MoM. Ultrasound study of the fetus shows nuchal translucency and a crown-rump length (CRL) of 6.49 cm (See Figures 4A and B below). Amniocentesis shows an elevated AFP and AChE. On physical exam, her vital signs are: blood pressure 121/80 mm Hg, pulse 115 beats per minute, respiratory rate 22 breaths per minute and temperature is 37°C (98.6°F). Her ultrasound findings are illustrated on Figures 4A and B.

## Case 5

A 3170-g (7 lbs) male infant was born at 40 weeks gestation to a 28-year-old (G1P0) by spontaneous vaginal delivery. At birth, he was noted to have a right-sided talipes equinovarus or clubfoot.

Mother's onset of menarche was at 13 years of age, and age of first intercourse was 19 years old with no history of sexually transmitted disease. Her medications include Singulair (montelukast), omeprazole and lamotrigine. Her past medical history includes bipolar disorder type 1, GERD, asthma, seasonal allergies, and a congenital seizure disorder. There is no history of familial congenital anomalies. A transvaginal ultrasound performed at 13 weeks gestation detected the plantar surface of the fetal foot in the same sagittal plane as both lower extremity bones (see Fig. 5). Fetal karyotyping showed a 46 XY chromosome.

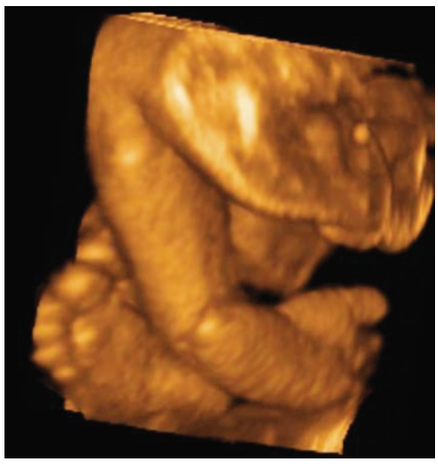


**Fig. 5:** 3D surface rendering of lower extremities

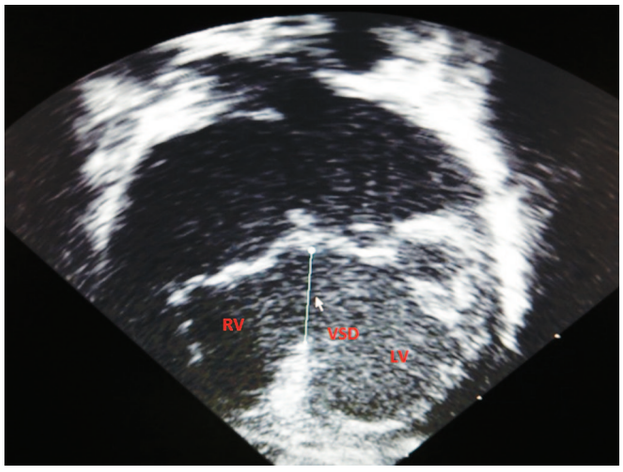



**Fig. 6:** Upper chamber view of the heart on 2D echocardiography

## Case 6

A 1-month old infant presents to the pediatric cardiologist office for follow-up evaluation of the echocardiogram finding shown in Figure 6.

The past medical history reveals that the infant was born to a 27-year-old (G3P1011) female at 38 weeks gestation. The murmur noted at birth prompted echocardiographic examination. The birth weight, height, and head circumference were all at the 50th percentile. The mother's past medical history includes frequent panic attacks, refractory bipolar disorder type 1 with a current manic episode, insomnia and fibromyalgia. Her medications include Lithium, Tylenol, Ambien and Advil. She began taking lithium before she was pregnant and continued the medication at the same dosage throughout her pregnancy because she was refractory to 1st and 2nd generation antipsychotics. Her serum lithium levels were stable throughout her pregnancy. There is no history of familial congenital anomalies. She had one normal spontaneous vaginal delivery 1 year ago and a spontaneous abortion 2.5 years ago.

The physical exam of the infant revealed a heart rate of 170 beats per minute, a 4/6 holosytolic murmur along the left lower sternal border with a palpable thrill, a pulse oximetry reading of 97% on room air with a hemoglobin concentration of 15 g/dl and no apparent cyanosis. EKG shows sinus tachycardia, evidence of right ventricular hypertrophy and right axis deviation. Figure 6 demonstrates echocardiography findings.

## Case 7

A 1-week-old Hispanic male infant was brought to the pediatric ward after experiencing blue lips and extremities. The boy was born from an uneventful delivery to a 26-year-old woman (G1P1) at 36 weeks gestation. The boy weighed 2.95 kg (6.5 lbs) at birth, with a head circumference and body length near the 30th percentile. The mother did not have a history of hypertension, diabetes or exposure to infectious or radiographic agents during her pregnancy.

Significant physical exam findings of the newborn revealed a heart rate of 200 beats per minute, a respiratory rate of 65, a pulse oximetry reading of 80% with a hemoglobin concentration of 15 g/dl with cyanosis of all extremities and lips. EKG showed a slurred upstroke QRS complex with a short PR interval. The echocardiogram is shown in Figure 7 below.

## Case 8

A 1-month-old male infant was brought to the pediatric clinic after reports of agitation, infantile colic, drowsiness,

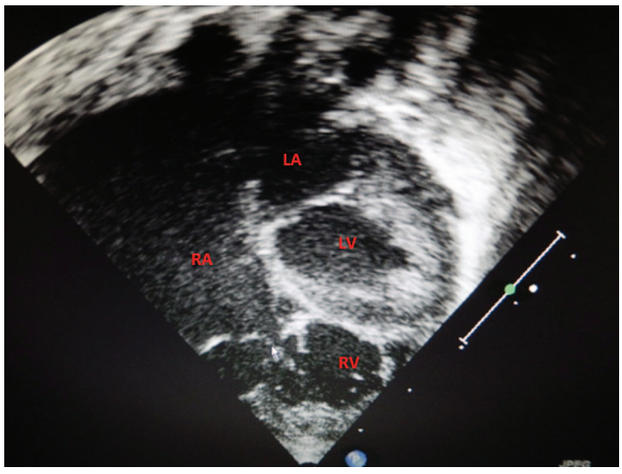



**Fig. 7:** Ebstein's anomaly: Four-chamber view of the heart on 2D echocardiography showing the septal leaflet of the tricuspid valve (arrow) displaced toward the apex of the right ventricle of the heart —finding consistent with Ebstein's anomaly in a newborn presenting with respiratory distress and cyanosis (RA: right atrium; RV: right ventricle; LA: left atrium; LV: left ventricle)

**Fig. 8:** Image of the baby presented in case 9. Holding the infant in horizontal suspension—the back hangs over the examiner's hand, and the limbs and head hang loosely

increased startle response, jitteriness and sleeplessness. Symptoms started at 1 week of age and have become progressively more severe with time and after breastfeeding. The boy was born term from an uneventful delivery to a 32-year-old woman (G1P1001). The boy weighed 3.63 kg (8.0 lbs) at birth, with a head circumference and body length near the 65th percentile. The mother did not have a history of hypertension, diabetes or exposure to infectious or radiographic agents during her pregnancy. However, the mother does have a history of major depressive disorder and anxiety. The mother is currently taking 75 mg of venlafaxine for depression and anxiety. There is no family history of any congenital abnormalities.

Physical exam of the infant shows: RR = 40 bpm, HR = 140 bpm, BP = 100/65 mm Hg. Temp = 37°C.

### Case 9

A 2-week-old female infant was brought to her pediatrician after experiencing hypotonia, lethargy, sucking difficulty, feeble cry and hypothermia. The baby girl was born at 38 weeks gestation to a (G1P1001) mother. During the delivery, the mother started having severe anxiety between contractions and was given a large bolus of benzodiazepines to calm her down. The boy weighed 6.0 lbs at birth (2.72 kg) with a head circumference and body length near the 20th percentile. The mother did not have a history of hypertension, diabetes or exposure to infectious or radiographic agents during the pregnancy. A picture of the infant is shown below (Fig. 8).

## DISCUSSION

### Case 1: Spontaneous Abortion

Fluoxetine is a selective serotonin reuptake inhibitor used most commonly as a first-line agent in the treatment of depression because of its safety records, high tolerability and its excellent efficacy. A database collected on the outcomes in pregnant women taking fluoxetine during their first trimester showed that 24.3% of women taking the pill and 25% of those women exposed to placebo had spontaneous abortions.[4] Figure 1 demonstrates heterogeneous material with abundant vascularity, typical of incomplete abortion.

The same database also showed that 3.6% of fluoxetine-exposed pregnancies and 16.7% of placebo-exposed pregnancies resulted in a major malformation. Therefore, there was no statistically significant differences in teratogenesis, preterm births or spontaneous abortions in fetuses/neonates of mothers taking fluoxetine when compared to the controls. In addition, pregnancy outcomes after exposure to sertraline, paroxetine, and fluvoxamine were described in a prospective series from nine teratology information centers in Canada and the United States. SSRI exposure was not associated with an increased risk of major congenital malformations.[42]

However, some studies indicate that paroxetine is associated with congenital heart defects, particularly VSDs and right ventricular outflow tract defects.[72-74] This finding may be due to a detection bias, since women on paroxetine during pregnancy received more prenatal ultrasound imaging compared to pregnant women not on paroxetine.

Neonates exposed to antidepressants during the second and third trimester should also be monitored for withdrawal symptoms after delivery, such as neonatal agitation, infantile colic, drowsiness, dyspepsia, increased startle response, jitteriness, sleeplessness and seizures. Late 2nd and 3rd trimester exposure to SSRIs (fluoxetine, paroxetine and sertraline) have been associated with a possible increased risk of persistent pulmonary hypertension of the newborn, although more studies need to be performed.[62]

NSAIDs use around the time of conception increases the risk of miscarriage, since NSAIDs prevent prostaglandins from promoting implantation.[43,44] Also, NSAIDs use after the second trimester increases risk of premature closure of the ductus arteriosus.

### Case 2: Cleft Lip with Benzodiazepines

The most common craniofacial malformation seen in the newborn is the cleft lip with or without the cleft palate or an isolated cleft palate. Orofacial clefts are diagnosed beginning after 12 weeks of gestation when the soft tissues of the fetal face can be clearly visualized sonographically and developmental separation of the lip and palate should no longer be present. Amniocentesis for fetal karyotype should be offered to women with ultrasound findings of fetal orofacial clefts and associated anomalies because of

the high rate of chromosomal defects. Fetuses found to have orofacial clefts should undergo careful assessment for additional structural abnormalities. Figure 2 demonstrates unilateral cleft lip imaged by 3D surface rendering.

Benzodiazepines are often used as an anxiolytic, an anticonvulsant, for muscle spasms, for acute ethanol withdrawal and for sedation. A meta-analysis of six different case-control studies found that fetal exposure to benzodiazepines was significantly associated with an elevated risk of an oral cleft (odds ratio 1.8).[77,78] This is controversial, as other studies have shown no association between benzodiazepines and birth defects.[79]

### Case 3: Limb Defects with Valproic Acid

Skeletal dysplasias are usually not life-threatening but can lead to severe cosmetic defects in the future child. Two-dimensional ultrasound is the primary imaging modality used for the initial assessment of a potentially affected fetus. When examining the limbs, one should determine if there is a pattern and degree of shortening and look for postural deformities, absence of limbs, length, shape (curvature), and whether there are any fractures and abnormal number of digits. This is best detected at 14 weeks of gestation or greater. Figures 3A and B demonstrate hypoplastic radius by 2D and 3D ultrasound.

Valproic acid, used as a first-line agent in tonic-clonic seizures, and also commonly used for bipolar disorder, has been associated with severe fetal malformations. A fetal valproate syndrome has been described, consisting of cardiovascular, craniofacial, urogenital, digital and respiratory tract abnormalities.[29-31] Valproic acid has also shown to cause limb defects in up to 36.8% of newborn infants of mothers taking the drug during pregnancy, including overlapping digits, talipes, clubfoot, clinodactyly, arachnodactyly, hip dislocation, and pre- and postaxial polydactyly.[32] Women with epilepsy should have precontraceptive counseling regarding the optimal anticonvulsant during pregnancy and switch to the least teratogenic and the lowest dose with the lowest number of medications needed. Valproic acid should be avoided in the first trimester of pregnancy, while choosing an alternate medication, such as a neuroleptic. For bipolar patients with major depression, the first line treatment is lamotrigine in adjunct with psychotherapy (Grade 2C). For patients who do not respond or tolerate lamotrigine, it is suggested that quetiapine be used. If refractory to these medications, the suggested therapy is fluoxetine + olanzapine, lamotrigine + lithium, or ECT. When it cannot be avoided, a reduction in daily doses as well as supplementation of 4 mg/day of folic acid should be given to reduce the risk of neural tube defects. In addition, one must carefully monitor serum valproic acid levels, perform ultrasonography and fetal echocardiography at 16 to 18 weeks' gestation to detect malformation early. Checking clotting parameters and administration of oral vitamin K (10 to 20 mg/day) during the last month of pregnancy are also recommended to protect against coagulopathies.[40,41]

### Case 4: Neural Tube Defects with Anticonvulsant Use

Neural tube defects are the second most common congenital anomaly in the US, only behind cardiac malformations. There have been three crucial factors that have led to an early detection and prevention of neural tube defects: (1) maternal screening to identify high risk pregnancies, (2) sonographic imaging combined with amniocentesis for diagnosis, and (3) administration of folic acid supplements.[45-47] There is a Grade 1B recommendation of screening for neural tube defects in all pregnant women at 15 to 20 weeks gestation via maternal alpha-fetoprotein levels and ultrasound. If there is a positive screening result then a combination of ultrasound and amniocentesis for acetylcholinesterase, alpha-fetoprotein and karyotype is performed. In cases where ultrasound imaging is not optional or is uncertain, MRI can be used to evaluate a neural tube defect *in utero*.[48] Two of the psychotropic medications that can lead to a folic acid deficiency, thereby predisposing to neural tube defects (such as spina bifida, myelocele, myelomeningocele, anencephaly) are carbamazepine and valproic acid, which can both be used for bipolar disorder. Many studies and case reports have indicated that carbamazepine exposure and valproic acid exposure can lead to a higher incidence of neural tube defects, developmental delays, craniofacial defects and behavioral changes.[28] Figures 4A and B show spina bifida visualized by 2D and 3D ultrasound.

### Case 5: Club Foot (Talipes Equinovarus) with Valproic Acid

Valproic acid, an anti-epileptic drug that can be used to treat bipolar disorder, works by increasing availability of GABA or mimic its action on postsynaptic receptor sites. As stated in case 3, Valproate has been shown to cause limb defects in up to 36.8% of newborn infants of mothers taking the drug during pregnancy, including overlapping digits, talipes, clubfoot, clinodactyly, arachnodactyly, hip dislocation and pre- and post-axial polydactyly.[32]

Clubfoot, or talipes equinovarus, refers to a developmental deformity of the foot in which one or both feet are excessively plantar flexed (equinus and varus at the ankle joint), with the forefoot swung medially (adduction at talonavicular

joint) and the sole facing inward (inversion at the subtalar joint). This occurs in both feet in up to 30 to 50% of cases. Ultrasound imaging, as early as 12 to 13 weeks of gestation, can detect the plantar surface of the fetal foot in the same sagittal plane as both lower extremity bones (Fig. 5).[49] When clubfoot is suspected, the sonographer should perform a complete anatomic survey, fetal echocardiogram and evaluate the intrauterine environment specifically looking for fetal compression or crowding by fibroids, amniotic bands, or synechiae. Some obstetricians recommend karyotyping via amniocentesis if an at-risk patient is not positive on ultrasound because of an increased risk of aneuploidy. If clubfoot is detected, there is no prenatal treatment and it does not change the antepartum or intrapartum management of the mother.

### Case 6: Lithium and Congenital Heart Disease

Mood stabilizers, such as lithium, carbamazepine and valproic acid, most often used for bipolar disorder have shown to be very problematic in pregnant and nursing women. These drugs freely cross the placenta and are present in nearly equal concentrations in maternal and fetal sera. Lithium in particular has been linked to an increased incidence of congenital cardiovascular anomalies, especially when taken during the first trimester.[14] Some of the cardiac anomalies associated with lithium use in pregnancy include Ebstein's anomaly, atrial septal defect, ventricular septal defect, pulmonary outflow obstruction, patent ductus arteriosus, coarctation of the aorta, mitral valve prolapse and a bicuspid aortic valve.[55-57] Figure 6 illustrates the ventricular septal defect (pointed by an arrow) measuring 1 cm on 1-day-old newborn (RV—right ventricle, LV—left ventricle, VSD—ventricular septal defect).

It is suggested that prenatal screening for anomalies using high-resolution ultrasound occur at 16 to 18 weeks for pregnant women on lithium. Depending on the results of the ultrasound, echocardiography screening should be performed before 20 weeks gestation.[11] It has also been suggested by Gelenberg that women who are psychiatrically stable that want to become pregnant should stop their lithium dosage at the beginning of the menstrual cycle in which they want to try and become pregnant, thus giving the lithium 2 weeks to clear the system.[8] Psychiatric relapse may also be delayed if the medication is tapered off rather than suddenly discontinued.[12] Serum lithium concentrations should be checked every 2 to 4 weeks during pregnancy, until 36 weeks gestation, at which point levels should be checked weekly. Women should avoid breastfeeding while taking lithium, since lithium is excreted in the breast milk at 40% of maternal serum levels, which can lead to lithium toxicity in the breast-feeding infant.[37,38]

A preliminary study has indicated that birth weight among lithium-exposed infants may be higher than in controls despite gestational ages.[13] Nephrogenic diabetes insipidus has also been reported in neonates whose mothers took lithium near term, although it resolved in 3 months.[15] Lithium can also cause fetal toxicity in the form of hypotonia, lethargy, poor reflexes, cardiac arrhythmias and difficulties in respiration.[16]

### Case 7: Lithium and Ebstein's Anomaly

Critical congenital heart disease is defined as lesions that require surgery or catheter based intervention in the first year of life. This is one of the leading causes of infant mortality, occurring in 25% of neonates with congenital heart disease.[51] Early diagnosis of neonatal congenital heart disease is difficult since clinical findings can be hard to detect, even with prenatal screening. Physical findings associated with CHD include abnormal cardiovascular examination (i.e. abnormal heart rate, abnormal precordial activity, abnormal heart sounds/pathologic murmurs, and diminished or absent peripheral pulses), presence of cyanosis, respiratory symptoms and noncardiac anomalies.[50]

Cyanosis is a bluish discoloration of the tissues that results when the absolute level of reduced hemoglobin in the capillary bed exceeds 3 g/dl, which generally corresponds to an oxygen saturation level below 85% in a neonate with a hemoglobin concentration of 15 g/dl. The appearance of cyanosis depends upon the total amount of reduced hemoglobin rather than the ratio of reduced to oxygenated hemoglobin.[52-54]

As stated above, lithium may cause congenital heart disease. Lithium has been linked to an increased incidence of congenital cardiovascular anomalies, especially when taking it during the first trimester.[14] In particular, Ebstein's anomaly, in which the tricuspid valve is displaced toward the apex of the right ventricle, has shown to have a 2.7% incidence in mothers who used lithium during the first trimester compared to a 0.005% incidence in the general population.[9,10] Echocardiography is the main imaging technique to diagnose Ebstein's anomaly. Figure 7 illustrates fetal echocardiography of Ebstein's anomaly in our patient. Note four-chamber view of the heart on 2D echocardiography showing the septal leaflet of the tricuspid valve (pointed by an arrow) displaced toward the apex of the right ventricle of the heart-finding consistent with Ebstein's anomaly in a newborn presenting with respiratory distress and cyanosis (RA—right atrium, RV—right ventricle, LA—left atrium, LV—left ventricle).

Additional findings include apical displacement of the septal tricuspid leaflet (by $\geq 8$ mm/m$^2$ compared to the position of the mitral valve), enlarged right ventricular

volume and low velocity tricuspid regurgitation.[59] Ebstein's anomaly can be classified as mild, moderate, or severe based upon the extent of apical displacement of the valve leaflets with resultant tricuspid regurgitation, and the degree of right-sided cardiac chamber dilation and dysfunction. Cardiac defects associated with Ebstein's anomaly include atrial septal defect, ventricular septal defect, pulmonary outflow obstruction, patent ductus arteriosus, coarctation of the aorta, one or more accessory conduction pathways, mitral valve prolapse and a bicuspid aortic valve.[55-58] A newborn with cyanosis should receive supportive therapy until the pulmonary vascular resistance drops and normalizes with time. Prostaglandin E1 infusion can also be used in cases of severe cyanosis to keep the patent ductus arteriosus open and increase pulmonary blood flow until the pulmonary vascular resistance drops. Surgical tricuspid valve repair or replacement with ASD closure is recommended if the neonate is symptomatic, has cyanosis ($O_2$ sat <90%), paradoxical embolus, cardiomegaly on chest X-ray, progressive RV dilation or reduction in RV systolic function.[59]

### Case 8: No Birth Defects with Venlafaxine

Venlafaxine, which inhibits 5-HT, NE, and Dopamine reuptake (SNRI) at the presynaptic neuron, is often used to treat major depression with anxiety. A study with a control of depressed pregnant women taking other antidepressants (such as SSRI's) compared with depressed pregnant women taking venlafaxine during the first trimester (after being cross matched for age, smoking and alcohol use) indicated that there is no statistically significant risk for major birth abnormalities above the baseline rate for women taking venlafaxine.[17] However, there have been reported cases of nonteratogenic effects because neonates have low hepatic drug metabolism and receive up to 9.2% of the maternal dose intake during breast feeding. Therefore, there can be neonatal withdrawal symptoms presenting as agitation, excessive crying (colic), drowsiness and dyspepsia, increased startle response, jitteriness, sleeplessness and seizures in infants of mothers exposed to antidepressants throughout their 2nd and 3rd trimesters.[60]

### Case 9: Benzodiazepines in the 3rd Trimester

Benzodiazepines are sedative-hypnotic agents used primarily for anxiety, seizure control, alcohol withdrawal, muscle relaxants and preanesthetic agents. Benzodiazepines bind to the GABA-A channel to increase chloride transmission thereby decreasing neural transmission, especially in the limbic system, thalamus and hypothalamus, to produce a calming effect. It is a pregnancy category D drug; therefore, it should only be used in life-threatening emergencies when no safer drugs are available. There has been some controversy over the 1st trimester effects of benzodiazepines. One study showed that maternal use of benzodiazepines during the 1st trimester can greatly increase the risk of severe congenital malformations, such as a cleft lip or palate.[18] One the other hand, a separate study by Rosenberg et al concluded that there was no statistical evidence that maternal use of diazepam during the first trimester can lead to an increased risk of cleft lip or cleft palate in the newborn.[19] An undisputed nonteratogenic adverse effect of benzodiazepine use during the third trimester of pregnancy or after a single large dose given just prior to delivery is floppy baby syndrome. This can present as hypotonia, lethargy, sucking difficulty, feeble cry, hypothermia and sometimes a low APGAR score and respiratory depression.[20] Figure 8 shows an example of a Floppy Baby Syndrome. The infant may assume a frog-like position when supine, with decreased spontaneous activity, and decreased muscle resistance to stretch. This is thought to be a withdrawal side effect from long-term exposure to benzodiazepines.[21-23] Therefore, it is suggested that women using long acting benzodiazepines (diazepam) during pregnancy should be gradually withdrawn from it during their last months of pregnancy, and should switch to a short acting benzodiazepines (lorazepam). It is also possible that behavioral teratogenesis may develop after benzodiazepine exposure *in utero*, which resembles fetal alcohol syndrome.[24] The exposed child might display delayed minor motor and mental development, including later learning disability, hyperactivity and perceptual disorders.[24-27,70] However, in the largest prospective study, benzodiazepine use was not linked to adverse neurobehavioral development in exposed children. Diazepam has been noted to have high milk to plasma ratio. Therefore, it should be avoided during breast feeding and shorter acting Lorazepam may be used instead.[6]

## REFERENCES

1. World population estimates by the US Census Bureau. USCB. Available at: http://www.census.gov/population/international/ (Retrieved on August 24, 2012).
2. Lamotrigine Pregnancy Registry: Interim Report. September 1, 1992 through March 31, 2001. Available at: http://pregnancyregistry.gsk.com/documents/lam_spring_2010_final_report.pdf (Accessed on October 18, 2013).
3. Lewis P. Drug usage in pregnancy. In: Lewis P, editor. Clinical pharmacology in obstetrics. Boston, Wright-PSG, 1983; p. 22-35.
4. Brendel K, Duhamel RC, Shepard TH. Embryotoxic drugs. Bio Res Pregnancy Perinatol 1985; 6:1-4.
5. Schou M, Weinstein MR. Problems of Lithium maintenance treatment during pregnancy, delivery and lactation. Agressolgie 1980; 21:714-716.
6. Briggs GG, Freeman RK, Yaffe SJ. Drugs in pregnancy and lactation. 2nd ed. Baltimore: Williams & Wilkins, 1986; p. 321-329.

7. Linden S, Rich CL. The use of lithium during pregnancy and lactation. J Clin Psychiatry 1983;44:358-365.
8. Gelenberg AJ. When a woman taking lithium wants to have a baby. Massachusetts General Hospital Newsletter. Biol Ther Psychiatry 1983;6:19-24.
9. Weinstein MR. Lithium treatment of women during pregnancy and the post-delivery period. In Johnson FN, editor. Handbook of Lithium Therapy. Lancaster, England: MTP Press 1980; p. 421-429.
10. Gelenberg AJ. Lithium-related congenital cardiac abnormalities: Prenatal screening. Massachusetts General Hospital Newsletter Biol Ther Psychiatry 1983;6:7-12.
11. Allan LD, Desai G, Tynan MJ. Letter: Prenatal echocardiographic screening for Ebstein's anomaly for mothers on lithium therapy. Lancet 1982;2:875-878.
12. Faedda GL, Tondo L, Baldessarini RJ. Outcome after rapid discontinuation of lithium treatment in bipolar mood disorders. Arch Gen Psychiatry 1993; 50:448-453.
13. Jacobson SJ, Jones K, Johnson K. Prospective multicentre study of pregnancy outcome after lithium exposure during first trimester. Lancet 1992; 339:530-533.
14. Schou M, Amdisen A. Letter: Lithium and placenta. Am J Obstet Gynecol 1975; 122:541-547.
15. Mizrahi EM, Hobbs JF, Goldsmith DI. Nephrogenic diabetes insipidus in transplacental lithium intoxication. J Pediatr 1979; 94:493-502.
16. Cohen D. Psychotropic medication in pregnancy. Advances in Psychiatric Treatment 2004;10:59-66.
17. Einarson A, Fatoye B, Sarkar M. Pregnancy outcome following gestational exposure to venlaxafine: A multicenter prospective controlled study. Am J Psychiatry 2001;158:1728-1733.
18. Safra MJ, Oakley GP. Association between cleft lip with or without cleft palate and prenatal exposure to diazepam. Lancet 1975;2:478-484.
19. Rosenberg L, Mitchell AA, Parsells JL. Lack of relation of oral clefts to diazepam use during pregnancy. N Engl J Med 1983; 309:1282-1285.
20. Cree JE, Meyer J, Hailey DM. Diazepam in labour: Its metabolism and effect on the clinical condition and thermogenesis of the newborn. BMJ 1973; 4:251-257.
21. Rementeria JL, Bhatt K. Withdrawal symptoms in the neonates from intrauterine exposure to diazepam. J Pediatr 1977; 90: 123-130.
22. Ananth J. Side effects on fetus and infant of psychotropic drug use during pregnancy. Int Pharmacopsychiatry 1976; 11:246-252.
23. Anderson PO, McGuire GG. Neonatal alprazolam withdrawal-possible effects of breast feeding. Drug Intell Clin Pharm 1989; 23:614-620.
24. Laegreid L, Olegard R, Wahlstrom J. Letter: Abnormalities in children exposed to benzodiazepines in utero. Lancet 1987; 1:108-115.
25. McDonald AD. Maternal health and congenital defect. N Engl J Med 1958; 258:767-772.
26. Pastuszak A, Schick-Boschetto B, Zuber C. Pregnancy outcome following first trimester exposure to fluoxetine (Prozac). JAMA 1993; 269:2246-2252.
27. Heinonen OP, Slone D, Shapiro S. Birth defects and drugs in pregnancy. Littleton, MA: PSG Publishing 1977; pp 345-347.
28. Altshuler L, Szuba M. Course of psychiatric disorders in pregnancy: dilemmas in pharmacological management. Neurol Clin 1994;12:6138.
29. DiLiberti JH, Faradon PA, Dennise NR. The fetal valproate syndrome. Am J Med Genet 1984 19:47380.
30. Winter RM, Donnai D, Burn J. Fetal valproate syndrome: Is there a recognizable phenotype? J Med Genet 1987;24:692-696.
31. Jager-Roman E, Deichi A, Jakob S. Fetal growth, major malformations and minor anomalies in infants born to women receiving valproic acid. J Pediatr 1986; 108:997-999.
32. Rodriguez-Pinilla E, Arroyo I, Foutevilla J. Prenatal exposure to valproic acid during pregnancy and limb deficiencies: a case control study. Am J Med Genet 2000;9:376-382.
33. McElhatton PR, Garbis HM, Elefant E, Vial T, Bellemin B, Mastroiacovo P, Aron J, Rodriguez-Pinilla E, Schaefer C, Pexieder T, Merlob P, Dal Verme S. The outcome of pregnancy in 689 women exposed to therapeutic doses of antidepressants: a collaborative study of the European Network of Teratology Information Services (ENTIS). Reproductive Toxicology 1996; 10:285-290.
34. Altshuler LL, Cohen L, Szuba MP, Burt VK, Gitlin M, Mintz J. Pharmacologic management of psychiatric illness during pregnancy: Dilemmas and guidelines. American Journal of Psychiatry 1996;153:592-606.
35. Ericson A, Kallen B, Wiholm BE. Delivery outcome after the use of antidepressants in early pregnancy. European Journal of Clinical Pharmacology 1999; 55: 503-508.
36. Hendrick V, Altshuler L. Management of major depression during pregnancy. American Journal of Psychiatry 2002;159: 1667-1673.
37. Winans EA. Antidepressant use during lactation. Journal of Human Lactation 2001;17:256-261.
38. Wisner KL, Perel JM, Findling RL. Antidepressant treatment during breast-feeding. American Journal of Psychiatry 1996; 153:1132-1137.
39. Dolovich LR, Addis A, Vaillancourt JM, Power JD, Koren G, Einarson TR. Benzodiazepine use in pregnancy and major malformations or oral cleft. Meta-analysis of cohort and case-controlled studies. BMJ 1998;317:839-843.
40. Bason L, Ming JE, Zackai EH. Intrauterine hemorrhage associated with prenatal valproate exposure. Am J Genet 1998; 64(Suppl 4):A159.
41. Iqbal MM, Gundlapalli SP, Ryan W. Effects of antimanic mood stabilizing drugs on fetuses, neonates and nursing infants. South Med J2001; 94:304-305.
42. Kulin NA, Pastuszak A, Sage SR. Pregnancy outcome following maternal use of the new selective serotonin reuptake inhibitors: a prospective controlled multicenter study. JAMA 1998; 279:609.
43. Li DK, Liu L, Odouli R. Exposure to nonsteroidal anti-inflammatory drugs during pregnancy and risk of miscarriage: population based cohort study. BMJ 2003;327:368.
44. Nielsen GL, Sorensen HT, Larsen H, Pedersen L. Risk of adverse birth outcome and miscarriage in pregnant users of nonsteroidal anti-inflammatory drugs: population based observational study and case-control study. BMJ 2001; 322:266-269.
45. Wald NJ, Cuckle H, Brock JH. Maternal serum-alpha-fetoprotein measurement in antenatal screening for anencephaly and spina bifida in early pregnancy. Report of UK collaborative study on alpha-fetoprotein in relation to neural-tube defects. Lancet 1977; 1:1323-1330.
46. Nicolaides KH, Campbell S, Gabbe SG, Guidetti R. Ultrasound screening for spina bifida: cranial and cerebellar signs. Lancet 1986;2:724.

47. Wald N, Cuckle H, Nanchahal K. Amniotic fluid acetylcholinesterase measurement in the prenatal diagnosis of open neural tube defects. Second report of the collaborative acetylcholinesterase Study. Prenat Diagn 1989; 9:813.
48. Saleem SN, Said AH, Abdel-Raouf M, et al. Fetal MRI in the evaluation of fetuses referred for sonographically suspected neural tube defects (NTDs): impact on diagnosis and management decision. Neuroradiology 2009; 51:761.
49. Keret D, Ezra E, Lokiec F, et al. Efficacy of prenatal ultrasonography in confirmed club foot. J Bone Joint Surg Br 2002;84:1015.
50. Romano-Zelekha O, Hirsh R, Blieden L, et al. The risk for congenital heart defects in offspring of individuals with congenital heart defects. Clin Genet 2001; 59:325.
51. Talner CN. Report of the New England Regional Infant Cardiac Program by Donald C. Fyler, MD, Pediatrics, 1980;65(suppl):375-461. Pediatrics 1998;102:258.
52. Lees MH. Cyanosis of the newborn infant. Recognition and clinical evaluation. J Pediatr 1970;77:484.
53. Dominquez Salgado M, Diaz-Obregon Santos MC, Santiago Gomez R, et al. Lamotrigine treatment as monotherapy during pregnancy. J Neurol 248(Suppl 2):146, 2001.
54. Morrow JI, Craig JJ, Russell AJC, et al. Epilepsy and Pregnancy: A Prospective Register in the United Kingdom. Post presented at the XVII World Congress of Neurology London, GBR, June, 2001.
55. Burchell HB, Dushane JW, Kilby RA, Wood EH. Ebstein's malformation: a clinical and laboratory study. Medicine (Baltimore) 1956;35:161.
56. Attenhofer Jost CH, Connolly HM, O'Leary PW, et al. Left heart lesions in patients with Ebstein anomaly. Mayo Clin Proc 2005; 80:361.
57. Watson H. Electrode catheters and the diagnosis of Ebstein's anomaly of the tricuspid valve. Br Heart J 1966; 28:161.
58. Sumner RG, Jacoby WJ Jr, Tucker DH. Ebstein's anomaly associated with cardiomyopathy and pulmonary hypertension. Circulation 1964; 30:578.
59. Shiina A, Seward JB, Edwards WD, et al. Two-dimensional echocardiographic spectrum of Ebstein's anomaly: detailed anatomic assessment. J Am Coll Cardiol 1984; 3:356.
60. Volpe JJ. Neurological examination: Normal and abnormal features. In: Neurology of the Newborn, 4th ed, WB Saunders, Philadelphia 2001. p.103.
61. Stewart DE. Clinical practice. Depression during pregnancy. N Engl J Med 2011; 365:1605.
62. FDA Drug Safety Communication: Selective serotonin reuptake inhibitor (SSRI) antidepressant use during pregnancy and reports of a rare heart and lung condition in newborn babies. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm283375.htm#data (Accessed on December 15, 2011).
63. Deligiannidis KM. Therapeutic drug monitoring in pregnant and postpartum women: recommendations for SSRIs, lamotrigine, and lithium. J Clin Psychiatry 2010;71:649.
64. Morrow J, Russell A, Guthrie E, et al. Malformation risks of antiepileptic drugs in pregnancy: a prospective study from the UK Epilepsy and Pregnancy Register. J Neurol Neurosurg Psychiatry 2006;77:193.
65. Holmes LB, Mittendorf R, Shen A, et al. Fetal effects of anticonvulsant polytherapies: different risks from different drug combinations. Arch Neurol 2011; 68:1275.
66. Holmes LB, Baldwin EJ, Smith CR, et al. Increased frequency of isolated cleft palate in infants exposed to lamotrigine during pregnancy. Neurology 2008;70:2152.
67. Einarson A, Boskovic R. Use and safety of antipsychotic drugs during pregnancy. J Psychiatr Pract 2009;15:183.
68. Yonkers KA, Wisner KL, Stowe Z, et al. Management of bipolar disorder during pregnancy and the postpartum period. Am J Psychiatry 2004;161:608.
69. Altshuler LL, Cohen L, Szuba MP, et al. Pharmacologic management of psychiatric illness during pregnancy: dilemmas and guidelines. Am J Psychiatry 1996;153:592.
70. Hartz SC, Heinonen OP, Shapiro S. Antenatal exposure to meprobamate and chlordiazepoxide in relation to malformations, mental development, and childhood mortality. N Engl J Med 1975; 292:726-729.
71. Meador KJ, Pennell PB, Harden CL. Pregnancy registries in epilepsy: a consensus statement on health outcomes. Neurology 2008; 71:1109-1113.
72. Alwan S, Reefhuis J, Rasmussen SA. Use of selective serotonin-reuptake inhibitors in pregnancy and the risk of birth defects. N Engl J Med 2007;356:26848.
73. Louik C, Lin AE, Werler MM. First-trimester use of selective serotonin-reuptake inhibitors and the risk of birth defects. N Engl J Med 2007;356:2675-2679.
74. Källén BA, Otterblad Olausson P. Maternal use of selective serotonin re-uptake inhibitors in early pregnancy and infant congenital malformations. Birth Defects Res A Clin Mol Teratol 2007;79:301-306.
75. Jentink J, Dolk H, Loane MA. Intrauterine exposure to carbamazepine and specific congenital malformations: systematic review and case-control study. BMJ 2010; 341:c6581.
76. Lindhout D, Höppener RJ, Meinardi H. Teratogenicity of antiepileptic drug combinations with special emphasis on epoxidation (of carbamazepine). Epilepsia 1984; 25:7782.
77. Dolovich LR, Addis A, Vaillancourt JM, et al. Benzodiazepine use in pregnancy and major malformations or oral cleft: meta-analysis of cohort and case-control studies. BMJ 1998; 317: 839-842.
78. Wikner BN, Stiller CO, Bergman U, et al. Use of benzodiazepines and benzodiazepine receptor agonists during pregnancy: neonatal outcome and congenital malformations. Pharmacoepidemiol Drug Saf 2007;16:1203-1205.
79. Koren G, Pastuszak A, Ito S. Drugs in pregnancy. N Engl J Med 1998; 338:1128-1131.

## SELF-ASSESSMENT QUIZ

1. **A 23-year-old female (G1P0) at her 25th week of pregnancy is in for her follow-up visit. She has been taking lithium for her bipolar disorder. She is also currently taking benzodiazepines, NSAIDs and sertraline. Her lithium levels are at therapeutic doses at the beginning of her pregnancy and have been kept at this level throughout the pregnancy. She is currently not on any folic acid supplementation. An ultrasound of the fetus was performed which showed a tricuspid valve that is displaced toward the apex of the right ventricle. All of the following could have prevented this disorder, except…**
   - **A.** Using the lowest effective dose of lithium.
   - **B.** Tapering off of the lithium starting 2 weeks before menstruation.
   - **C.** Using monotherapy instead of polydrug therapy.
   - **D.** Supplementing with 4 mg of folic acid.
2. **A 32-year-old female (G2P2002) recently delivered a term newborn girl and has been breast feeding the baby girl for 2 weeks. The newborns height, weight and head circumference are all around the 45$^{th}$ percentile. The mother recently noticed that the baby has been agitated, has an increased startle response, is drowsy, has dyspepsia, has not been sleeping lately and started having seizures starting this morning. Which maternal drug could most likely be the culprit?**
   - **A.** Benzodiazepine
   - **B.** Venlafaxine
   - **C.** Lithium
   - **D.** Cocaine use
3. **A 30-year-old female (G0P0) is planning on trying to get pregnant within the next month. She is currently taking benzodiazepine for anxiety, as well as sertraline for depression and warfarin for chronic atrial fibrillation. What should you tell her regarding the risk of her fetus developing a congenital anomaly or having an adverse effect from the medication?**
   - **A.** Benzodiazepine has shown to be associated with talipes equinovarus.
   - **B.** Sertraline may cause Ebstein's anomaly, a defect of the heart.
   - **C.** Chronic benzodiazepine use has been associated with floppy baby syndrome.
   - **D.** Warfarin has been associated with neural tube defects.
4. **A healthy 30-year-old (G2P0010) women presents to your office with concerns about having a baby with spina bifida. She is currently in her 16th week of gestation. Two years ago she had a baby with anencephaly that died shortly after delivery. Ever since then, she has been increasingly cautious about getting pregnant again, since she is afraid of losing another child. She is currently taking acetaminophen, valproic acid and sertraline. She has a past medical history of anxiety, epileptic seizures and bipolar disorder type 1. Upon performing a transvaginal ultrasound it was noted that the fetus had a nuchal translucency. What is the next best step in management?**
   - **A.** Discuss pregnancy termination options with the patient
   - **B.** Amniocentesis for a fetal AChE and AFP levels
   - **C.** Do nothing and comfort the patient by informing her that this is a normal finding and she has very little risk for another congenital neural tube defect in her child
   - **D.** Amniocentesis for a Karyotype
5. **A 6 lb 5 oz (2.86 kg) newborn is delivered from a healthy 36-year-old female (G2P2002) vaginally with an APGAR score of 4 at 1 minute and a score of 8 at 5 minutes. One day after birth, the neonate has hypotonia, lethargy, sucking difficulty, feeble cry and hypothermia. The pregnancy was a normal vaginal delivery with no complications. The mother denies any viral infections during her pregnancy and denies any STDs or drug use. The mother has been craving honey and has been eating it throughout her pregnancy. Also, the mother does have a past medical history of major depression and had been taking sertraline at a low dose during pregnancy. Just before delivery the anesthesiologist gave a single dose bolus of Diazepam to calm the patient down because she started to panic. What is the most likely cause of this babies symptoms?**
   - **A.** Chronic sertraline use during pregnancy
   - **B.** Spinal muscular atrophy
   - **C.** Diazepam bolus administered during delivery
   - **D.** Infant botulism
6. **A 1-month-old infant presents to the pediatrician's office with polyuria, excessive nocturia and what appears to be polydipsia. The infant's urine osmolarity is measured at 400 mOsm/kg. The 26-year-old (G1P1) mother has a recent history of refractory bipolar disorder, for which she was started on lithium during her last trimester of pregnancy. What is the most likely diagnosis?**
   - **A.** Nephrogenic diabetes insipidus
   - **B.** Lithium induced diabetes mellitus type 1
   - **C.** Vasopressin V2 receptor gene mutation
   - **D.** Congenital anomalies of the urogenital system leading to a UTI
7. **A 23-year-old (G2P1001) patient comes to your office at 17 weeks gestation to review the results of her triple test done 1 week ago. You tell the patient that her MSAFP levels are elevated at 2.0 MOM. The patient's past medical history consists of bipolar disorder and epileptic seizures treated with carbamazepine. Her past obstetrical history is a normal vaginal delivery 1 year ago without any complications. What is the next best step in management?**
   - **A.** Perform a fetal ultrasound
   - **B.** Offer the mother a chorionic villus sampling to obtain a fetal karyotype
   - **C.** Inform the mother that her child has a neural tube defect
   - **D.** Tell the mother that the blood tests are most likely false positive results and that repeat testing needs to be performed at 23 weeks gestation.
8. **A 32 yo G3P2 in her 5th week gestation has been taking valproic acid for her tonic-clonic seizures and for her diagnosis of bipolar type 1 disorder. She has been taking prenatal vitamins and 4 mg/day of folic acid. Her previous two pregnancies were uncomplicated and both babies were born term. Which of the following is this patient's fetus most likely NOT at risk for developing?**
   - **A.** Spina bifida
   - **B.** Craniofacial abnormality

**C.** Talipes equinovarus
**D.** Floppy baby syndrome

**9. A 29-year-old G1P0 female in her 20th week of gestation has recently lost interest in her yoga classes, which she used to enjoy, and cries every day. She feels increasingly tired and takes several naps per day. She feels slower than usual and feels that her arms are getting heavier. She denies any suicidal ideation. She has no acute life stressors aside from the pregnancy. She has a good support system in place. Which of the following is the best treatment modality for this patient?**
**A.** Begin cognitive behavioral therapy
**B.** Begin fluoxetine 20 mg/daily
**C.** Perform electroconvulsive therapy
**D.** This is expected for a newly pregnant women and no therapy should be initiated.

**10. A 26-year-old woman is brought into the ER by her friends because she has been acting strange for the past 2 to 3 weeks. She has not slept more than 1 hour per day, she has been buying countless shoes and clothing online with money she does not have, she has been talking very rapidly, and she has been sexually promiscuous with multiple partners with no protection in the past 2 months. STD testing came back negative but her β-hCG was positive and ultrasound confirmed a viable pregnancy. Which of the following medications will have the least teratogenic effects on the fetus, while also most effectively treating the mother's disorder?**
**A.** Haloperidol
**B.** Lamotrigine
**C.** Olanzapine
**D.** Lithium

**Correct Answers:**
**1. D; 2. B; 3. C; 4. B; 5. C; 6. A; 7. A; 8. D; 9. A; 10. A**

# *Submitting a paper to* Donald School Journal of Ultrasound in Obstetrics and Gynecology

Authors should submit their manuscripts to Editors-in-Chief either by regular mail or through e-mail, see details below:

*Note to authors:* Please make sure your contact address is clearly visible on the outside of all packages you are sending to the Editors.

Papers are accepted for consideration on condition that you will accept and warrant the following conditions. In order to ensure both the widest dissemination and protection of material published in our Journal, we ask authors to assign the rights of copyright in the articles they contribute. This enables Jaypee Brothers Medical Publishers (P) Ltd. to ensure protection against infringement.

1. It is a condition of the publication that authors vest or license copyright in their articles, including abstracts, in Jaypee Brothers Medical Publishers (P) Ltd. This enables us to ensure full copyright protection and to disseminate the article, and the journal, to the widest possible readership in print and electronic formats as appropriate. Authors may, of course, use the material elsewhere after publication providing that prior permission is obtained from Jaypee Brothers Medical Publishers (P) Ltd.
2. We shall prepare and publish your Article in the Journal. We reserve the right to make such editorial changes as may be necessary to make the Article suitable for publication; and we reserve the right not to proceed with publication for whatever reason. In such an instance, copyright in the Article will revert to you.
3. You hereby assert your moral rights to be identified as the author of the Article according to Copyright laws.
4. You warrant that you have secured the necessary written permission from the appropriate copyright owner or authorities for the reproduction in the Article and the Journal of any text, illustration, or other material. You warrant that, apart from any such third party copyright material included in the Article, the Article is your original work, and cannot be construed as plagiarizing any other published work, and has not been and will not be published elsewhere.
5. In addition, you warrant that the Article contains no statement that is abusive, defamatory, libellous, obscene, fraudulent, nor in any way infringes the rights of others, nor is in any other way unlawful or in violation of applicable laws.
6. You warrant that, wherever possible and appropriate, any patient, client or participant mentioned in the text has given informed consent to the inclusion of material pertaining to themselves, and that they acknowledge that they cannot be identified via the text.
7. If the Article was prepared jointly with other authors, you warrant that you have been authorized by all coauthors to sign this Agreement on their behalf, and to agree on their behalf the order of names in the publication of the Article.
8. You shall keep us and our affiliates indemnified in full against all loss, damages, injury, costs and expenses (including legal and other professional fees and expenses) awarded against or incurred or paid by us as a result of your breach of the warranties given in this agreement.
9. You undertake that you will include in the text of the Article an appropriate statement should you have a financial interest or benefit arising from the direct applications of your research.
10. If the Article was prepared jointly with other authors, you warrant that you have been authorized by all coauthors to sign this Agreement on their behalf, and to agree on their behalf the order of names in the publication of the Article. You shall notify us in writing of the names of any such co-owners.
11. This agreement (and any dispute, proceeding, claim or controversy in relation to it) is subject to Indian law and the jurisdiction of the Courts of New Delhi. It may only be amended by a document signed by both of us.

There are no page charges in *Donald School Journal of Ultrasound in Obstetrics and Gynecology.*

*Editors-in-Chief*

Professor Asim Kurjak, Department of Obstetrics and Gynecology, University of Zagreb Medical School, Sveti Duh Hospital, Sveti Duh 64 10000 Zagreb, Croatia. *Phone:* + 385-1-3745-537, *Fax:* + 385-1-3745-534, *e-mail:* asim.kurjak@public.carnet.hr

Professor Frank A Chervenak, Given Foundation Professor and Chairman, Department of Obstetrics and Gynecology, New York Presbyterian Hospital- New York Weill Cornell Center, 525 East 68th Street, Room J-130, New York, NY 10021, USA. *Phone:* +12127463184, *Fax:* +12127463378 *e-mail:* fac2001@med.cornell.edu

For more information on our journals and books publishing, visit our Jaypee Brothers Website
www.jaypeejournals.com, www.jaypeebrothers.com

If you are unable to access the website please write to:
Journals Department, Jaypee Brothers Medical Publishers (P) Ltd., 4838/24 Ansari Road, Daryaganj, **New Delhi** 110 002, India
*Phone:* +91-11-43574357
*Fax:* +91-11-43574314
*e-mail:* subscriptions@jaypeejournals.com