Use of Antidiabetic, Antihypertensive, and Psychotropic Drugs in Pregnancy

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ANTIDIABETIC DRUGS

Pregnancy in women with preexisting diabetes is characterized by lower glucose levels and lower insulin requirements which changes quickly as insulin resistance increases exponentially during the second and early third trimesters then levels off toward the end of the third trimester. Treatment needs to be adjusted appropriately to avoid hyperglycemia for women with gestational diabetes mellitus (GDM) or preexisting diabetes [1S]. Although some small randomized controlled trials have shown efficacy and short-term safety of metformin and glyburide for the treatment of GDM, insulin is still the first-line recommended treatment of GDM. Moreover, the current insulin preparations have not been shown to cross the placenta [2c, 3M, 4c]. Currently, insulin analogs used in clinical practice are mature two-chain peptides which possess different pharmacokinetic profiles [5H].

Metformin is a biguanide that work by inhibiting glucose production in the liver, decreases the absorption of glucose in the intestine, and stimulates glucose uptake in the peripheral tissues. Glyburide is a sulfonylurea that binds to the beta cells of the pancreas and increases insulin secretion and insulin sensitivity of the peripheral tissues. Both metformin and glyburide have been recommended for the treatment of GDM, but there are some safety concerns that are regarding the use of these oral agents. While insulin does not cross the placenta, both metformin and glyburide cross the placenta which presents long-term safety concerns. The American College of Obstetricians and Gynecologists (ACOG) states that metformin crosses the placenta with levels that can be as high as the maternal concentrations [6S]. Also, according to the American Diabetes Association (ADA), about 70% of maternal levels of glyburide cross the placenta. It is still questionable if these drugs used in the treatment of diabetes in pregnancy are as safe and effective as insulin [1S].

Pregnant women with GDM have high risk of preeclampsia, maternal weight gain, pregnancy induced hypertension, and respiratory distress syndrome (RDS). Some studies have also reported cases of depression, and incidence of cesarean section. Also, children born to mothers with GDM are at higher risk of macrosomia, large for gestational age (LGA), admission to the neonatal intensive care unit (NICU), perinatal mortality (fetal and neonatal death), hypoglycemia, jaundice, weight gain and increased risk of developing type 2 diabetes [7M]. Feig et al. claimed that poor glycemic control in mothers with diabetes increases the risk of respiratory distress syndrome, neonatal hypoglycemia and NICU admissions [8c].

Allergic Reactions

The risk of allergic reactions to insulin administration during pregnancy is uncommon with only 20 reported cases worldwide [9A]. Recently, three cases of patients who presented with localized reactions at subcutaneous

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injection sites within 1 week of treatment with insulin detemir for GDM were reported [9A]. In the first case, a 32-year-old pregnant woman of Chinese descent, who was given 20 units of detemir at 34 weeks gestation, noted pruritic, painful, erythematous reactions developing at the injection site the previous night. Similarly, a 26-year-old pregnant woman of Indian descent with GDM who was given detemir at 28 weeks gestation noticed generalized pruritus as well as tender, painful, erythematous nodules that appeared approximately 8 h after each insulin injection. For both cases, the allergic reaction resolved over a period of 4–5 days. The third case was a 39-year-old pregnant woman of Chinese descent who also noted the development of pruritic tender erythematous nodules 24 h after injecting detemir in her thighs. There were no further reactions at injection sites on changing to insulin glargine. However, it is possible that the allergic reactions may be due to non-insulin additives in the detemir preparations and to reactions to natural rubber latex in the insulin vial membrane [9A].

Shoulder Dystocia

A retrospective study of 19 236 births that occurred between April 1, 2011 and July 25, 2013 in five hospitals located in different states (Wisconsin, Florida, Maryland, Michigan, and Alabama) reported that only births to the women treated with insulin were at an increased risk of shoulder dystocia (odds ratio = 2.10, 9 confidence interval [1.01, 4.37]) as opposed to women treated with other glycemic agents or through diet [10C]. Shoulder dystocia is a perinatal complication which occurs when a fetus's shoulders fail to exit the birth canal after the head [10C].

Neonatal Outcomes

Macrosomia

In a pairwise meta-analysis of 32 randomized controlled trials (RCTs), 25 studies involving 3412 patients with GDM showed that the incidence of macrosomia for metformin compared to insulin was significantly lower (OR, 0.729; 95% CI, 0.545–0.974) [7M]. Macrosomia was also significantly lower for metformin compared with glyburide (OR, 0.5411; 95% CI, 0.2385–0.9855) based on the network meta-analysis. These findings indicate that metformin has the lowest risk of macrosomia [7M]. In a prospective randomized controlled study comparing metformin to glyburide, the women with GDM in the glyburide group (glyburide 2.5–20 mg/day 30 min before a meal and/or at 10:00 P.M.) showed higher incidence of macrosomia than the women in the metformin (850–2550 mg/day right after meals and/or at 10:00 P.M.) group [11c]. A possible explanation is that glyburide readily crosses the placenta [11c]. A meta-analysis of pregnant women with polycystic ovary syndrome that included 13 studies involving 1606 pregnant women, only 1 study provided macrosomia data. The 1 study reported the rate of macrosomia was 0 in the metformin group compared to 12.5% in the placebo group [12M]. Although the abovementioned meta-analyses have indicated that glyburide was associated with a higher incidence of macrosomia, a meta-analysis that included 10 randomized control trials involving 1194 women with GDM indicated that the risk of macrosomia [RR, 1.69; 95% CI, 0.57–5.08; $P = 0.35$] did not differ between the glyburide group and insulin group [13M]. However, when the newest and largest trial was excluded from the analysis due to the use of a lower dose (0.2 U/kg), the findings indicated macrosomia occurred significantly more often with the glyburide group than insulin group [13M].

Large for Gestational Age (LGA)

According to a meta-analysis from 15 randomized control trials that involved 1813 patients with GDM, the incidence of LGA for metformin was significantly lower than insulin (OR, 0.647; 95% CI, 0.438–0.956) and glyburide (OR, 0.431; 95% CI, 0.229–0.814) [7M]. Song et al. reported that the incidence of LGA for glyburide actually increased, but there was no significant difference in the incidence of LGA between glyburide and insulin [RR, 2.54; 95%CI, 0.98–6.57; $P = 0.05$] [13M].

Hypoglycemia

Neonatal hypoglycemia occurs when in the first 24 h post-delivery the blood glucose is less than 40 mg/dL or in the second day of life the blood glucose is less than 50 mg/dL [11c]. Comparing insulin and the oral antidiabetics, a pairwise meta-analysis that included 26 studies involving 3360 patients with GDM indicated that metformin had lower incidence of neonatal hypoglycemia than insulin (OR, 0.636; 95% CI, 0.486–0.832), and insulin was lower than glyburide (OR, 0.647; 95% CI, 0.423–0.991) [7M]. Similarly, based on network meta-analysis, metformin was significantly lower compared to insulin (OR, 0.6331; 95% CI, 0.3987–0.9331), and glyburide (OR, 0.3898; 95% CI, 0.1989–0.6558), but insulin was significantly lower than glyburide (OR, 0.6236; 95% CI, 0.3464–0.9992) [7M]. Moreover, a prospective randomized controlled study involving 53 patients being treated with glyburide and 51 with metformin reported that glyburide was associated with higher incidence of neonatal hypoglycemia [11c].

Preterm Birth

Based on a recent review, the largest study of metformin use in GDM (MiG) trial involving 751 women with GDM reported metformin with a higher incidence of

preterm birth (12.1% vs 7.6%; $P=0.04$) compared to insulin [14R]. The women on the metformin group were started at 500 mg once or twice daily and titrated to a maximum of 2500 mg as necessary plus insulin when required [14R]. However, a network meta-analysis that included 32 randomized controlled trials showed that glyburide, compared to metformin and insulin, has the highest incidence of preterm birth [7M].

Birth Weight

For birth weight, a meta-analysis of 32 studies with 4060 GDM patients indicated that glyburide is ranked worst with higher mean birth weight compared to metformin and insulin [7M]. The pairwise meta-analysis showed that the mean birth weight for metformin was significantly lower than that for insulin (SMD, 0.111; 95% CI, 0.194–0.028) and glyburide (SMD, 0.235; 95% CI, 0.399–0.071). Also, the mean birth weight for insulin was significantly lower when compared to that of glyburide (SMD, 0.180; 95% CI, 0.327–0.033). Based on network meta-analysis, it was also observed that metformin had significantly lower birth weight compared to glyburide (SMD, 0.2591; 95% CI, 0.4383–0.08446) [7M]. Contrary to most meta-analyses, a recent meta-analysis of 10 randomized control trials involving 1194 participants reported no significant difference in birth weight between the GDM patients in the glyburide group and the insulin group [mean difference (MD), 79; 95% CI, −64 to 221.99; $P=0.28$] [13M]. The study further concluded that glyburide is safe and effective for use in GDM [13M]. A retrospective study of 820 GDM pregnancies treated between January 2011 and September 2014 in a university and non-university hospital compared the pregnancy outcomes between two treatment groups: diet-only and additional insulin therapy [15c]. The results have shown that neonates born in the insulin-group had a lower birth weight compared with the diet-group (3364 vs 3467 g, $P=0.005$) [15c].

Other Neonatal Outcomes

In a pairwise and network meta-analyses of 13 studies which included 2008 GDM patients, the findings showed no significant difference between the metformin, insulin, and the glyburide groups for the incidence of RDS [7M]. Similarly, the pair-wise and network meta-analysis showed no significant difference between the metformin, insulin, and the glyburide groups for the incidence of hyperbilirubinemia [7M]. Moreover, a systematic review that looked at the risk of hyperbilirubinemia in infants whose mothers had been treated with metformin or glibenclamide reported that there was no significant difference between the groups (RR 0.68, 95% CI 0.37–1.25; two studies, $n=205$ infants) [16R].

Preeclampsia

A meta-analysis of 10 randomized control trials involving 1194 participants showed no differences in the risk of preeclampsia [RR, 0.98; 95% CI, 0.56–1.74], a primary indicator of maternal outcome [13M]. The meta-analysis included women with GDM who were not controlled with lifestyle modifications and thus required drug treatment. The treatment schedule in the control was insulin and the interventional group was glyburide [13M]. This result was consistent with the findings of a previous meta-analysis of 11 studies that involved 1754 GDM patients [7M].

ANTIHYPERTENSIVE DRUGS

According to The American College of Obstetricians and Gynecologists (ACOG), hypertensive disorders in pregnancy include preeclampsia, eclampsia, chronic hypertension (existing prior to pregnancy), chronic hypertension with superimposed preeclampsia, and gestational hypertension (elevated blood pressure after 20 weeks of gestation without evidence of preeclampsia) [17S]. Globally, a major cause of both maternal and perinatal morbidity and mortality is hypertensive disorders which complicate about 10% of pregnancies [17S]. Treatment of chronic hypertension in pregnancy is complicated by concerns that excessive lowering of blood pressure can negatively affect the fetus and a lack of good quality evidence for specific treatment thresholds [17S]. ACOG recommends the use of antihypertensive drug for pregnant women with systolic blood pressure greater or equal to 160 mmHg and a diastolic blood pressure greater or equal to 105 mmHg [17S]. Recommendations for pharmacologic therapy identify labetalol, nifedipine, and methydopa as preferred above all other options [17S]. Renin–antgiotensin system blockers and mineralocorticoid receptor antagonists are explicitly recommended against [17S]. The ACOG 2017 Committee Opinion on Emergent Therapy for Acute Onset, Severe Hypertension During Pregnancy and the Postpartum period recommends administration of intravenous labetalol, intravenous hydralazine, or oral immediate release nifedipine for prevention of maternal stroke within 30–60 min of diagnosis of severe hypertension [18S].

Two studies have reported on analysis of data from The National Birth Defects Prevention Study (NBDPS) for risk of cardiac malformation in infants exposed in utero to antihypertensive drugs. NBDPS is a population-based, case–control study in the United States. The 2009 publication in Hypertension by Caton et al. analyzed data from pregnancies with estimated due dates from 1997 to 2003 [19C]. There were 5021 cases and 4796 controls [19C]. In 2017,

Fisher et al. published a follow-up analysis of NBDPS data for pregnancies with estimated due dates from 2004 to 2011 [20C]. The analysis included 10 625 cases and 11 137 controls [20C]. As in the 2009 publication sample [19C], cases were more likely to be older, overweight or obese, and report cigarette smoking [20C]. Early pregnancy antihypertensive use and late pregnancy antihypertensive use and untreated hypertension were associated with statistically significant increased risk of coarctation of the aorta (CoA), pulmonary valve stenosis (PVS), perimembranous ventricular septal defects (VSD-PM), and secundum atrial defects (ASD2) [20C]. Analysis of association by class was performed for beta-blockers, renin–antgiotensin system blockers, centrally-acting antiadrenergics, diuretics and calcium channel blockers [20C].

Any Antihypertensive Drug

Coarctation of the Aorta (CoA)

No significant risk increase was shown for CoA in the analysis of exposure during the first trimester to specific classes or specific drugs in the 2009 analysis of NBDP data [19C]. Exposure to any antihypertensive drug in the first trimester did show an increase in CoA OR 3.0; 95% CI, 1.3–6.6) [19C]. The 2017 analysis of NBDP data showed an increase in CoA for both early and late exposure to any antihypertensive (OR 2.5; 95% CI, 1.52–4.11 and OR 2.31; 95% CI, 1.26–4.24) [20C].

Pulmonary Valve Stenosis (PVS)

Both first trimester and late in pregnancy exposure to any antihypertensive were associated with an increased risk of PVS (OR 2.6; 95% CI, 1.3–5.4 and OR 2.4; 95% CI, 1.1–5.4) [19C]. The 2017 analysis of NBDP data showed an increase in PVS for both early and late exposure to any antihypertensive (OR 2.19; 95% CI, 1.44–3.34 and OR 1.93; 95% CI, 1.10–3.37) [20C].

Ebstein Malformation

First trimester exposure to any antihypertensive showed increased risk of Ebstein malformation (OR 11.4; 95% CI, 2.8–34.1) [19C]. The 2017 analysis of NBDPS data also showed an increased risk of Ebstein malformation with early pregnancy exposure to any antihypertensive (OR 3.89; 95% CI, 1.51–10.06) [20C].

Septal Defects: Perimembranous Ventricular Septal Defects (VSD-PM) and Secundum Atrial Defects (ASD2)

Risk of ASD2 was increased for exposure to any antihypertensive in both the first trimester and late in pregnancy initiation (OR 2.4; 95% CI, 1.3–4.4 and OR 2.4; 95% CI, 1.3–4.4.) [19C]. Risk of VSD-PM was only increased with late initiation of antihypertensives (OR 2.3; 95% CI, 1.2–4.6) [19C]. The 2017 analysis of NBDPS data also shows and increased risk of ASD2 with exposure to any antihypertensive in early and late pregnancy (OR 1.94; 95% CI, 1.36–2.79 and OR 2.61; 95% CI, 1.75–3.89) [20C]. There was also an increased risk of VSD-PM associated with exposure to any antihypertensive in both early and late pregnancy (OR 1.90; 95% CI, 1.09–3.31 and OR 1.85; 95% CI, 1.02–3.37) [20C].

Beta-Blockers

The 2009 analysis of NBDPS showed an increase risk of PVS with first trimester use of beta-blockers (OR 5.0; 95% CI, 1.8–13.8) [19C]. Analysis of exposure to atenolol and labetalol specifically did not show a statically significant increase [19C]. In the 2017 analysis of NBPDPS data beta-blockers were associated with an increased risk of CoA (OR 2.61; 95% CI, 1.25–5.45), PVS (aOR, 3.03; 95% CI, 1.68–5.46), VSD-PM (aOR, 4.13; 95% CI, 1.82–9.37) and ASD2 aOR, (2.35; 95% CI, 1.37–4.04) [20C]. Labetalol was used by 43.8% of cases and 42.5% of controls exposed to beta blocker in early pregnancy and the defects reported were the same as for the class [20C].

Centrally-Acting Adrenergic Agents

Cardiovascular Effects

The 2009 analysis of NBDPS data showed an increase risk of Ebstein malformation with use of any centrally-acting antiadrenergic (OR 16.9; 95% CI, 3.0–62.1) and methyldopa specifically (OR 12.7; 95% CI, 1.4–58.3) with first trimester exposure [19C].

A case report published in 2014 describes hypertensive crisis and acute cardiac failure in a 2-week-old infant [21A]. No immediate underlying cause was identified [21A]. The mother had begun treatment for gestational hypertension with methyldopa 500 mg twice daily at 27 weeks gestation [21A]. At 30 weeks gestation the methyldopa dose was increased to 500 mg three times daily which controlled maternal blood pressure until cesarean delivery at 37 weeks gestation [21A]. Upon delivery the infant was small for gestational age and experiencing respiratory distress requiring admission to the neonatal intensive care [21A]. She was then discharged after a week [21A]. At 2 weeks of age she presented to the emergency department and was diagnosed with hypertensive crisis and acute cardiac failure which required admission to the pediatric intensive care unit (PICU) [21A]. The total duration of hospitalization was 2 weeks with 1 week spent in the PICU [21A]. The final diagnosis was withdrawal effects due to in utero exposure to methyldopa [21A].

Hepatitis

Another case report published in 2014 describes a 34-year-old woman who presented with severe jaundice

and hepatitis at 8 weeks after delivering her fourth child [22A]. No previous history of hypertensive disorders in pregnancy, renal disease, or chronic hypertension [22A]. During this fourth pregnancy she was diagnosed with preeclampsia at 24 weeks gestation [22A]. Methyldopa 500 mg three times daily and hydralazine 50 mg three times daily were used to treat her hypertension [22A]. Delivery was induced at 38 weeks due to severe preeclampsia [22A]. Three weeks after delivery her nephrologist discontinued hydralazine and reduced the dose of methyldopa to 250 mg three times daily [22A]. Liver function tests during pregnancy were within normal limits [22A]. She presented for her 8 weeks postpartum check-up with signs of jaundiced and lethargic and methyldopa was discontinued [22A]. The patient had no personal or family history of liver disease, no IV drug use or alcoholism [22A]. After excluding other causes, she was diagnosed with methyldopa induced hepatitis [22A]. Two months later liver function tests had decreased to near normal levels but residual hepatic fibrosis remained [22A].

Preterm Birth

This prospective observational cohort study was established to assess the degree of major birth defects and spontaneous abortions in pregnant women taking methyldopa for chronic hypertension [23C]. The German Embryotox pharmacovigilance institute evaluated the outcomes due to exposure to methyldopa in the first trimester of pregnancy [23C]. The study examined patients from January 1, 2000 to December 31, 2014 [23C]. Of those patients in the German Embryotox pharmacovigilance institute who were exposed to antihypertensive drugs, 261 of them were pregnant women who were exposed to methyldopa during their first trimester and had complete follow-ups done throughout their pregnancies to assess pregnancy outcome [23C]. The control group consisted of 526 random pregnant women without chronic hypertension [23C]. Most baseline characteristics between both groups were similar with the exception of maternal BMI which was elevated in the methyldopa cohort (mean BMI, 28 mg/m^2 vs 23 mg/m^2) [23C]. This case cohort also included fewer women with an academic education and less smokers (8% vs 17%) [23C]; the medium dose was 500 mg daily and about 54% of women were on methyldopa prior to conception [23C]. About 127 women in their first trimester were on single therapy methyldopa [23C]. Results showed a higher cumulative incidence of spontaneous abortions in the methyldopa cohort compared to the control; however, this was not statistically significant (17% vs 13%) [23C]. Elective terminations occurred less frequently in the methyldopa group [23C]. Females in this group also had a higher likelihood of developing gestational diabetes mellitus, abruption placentae, and Cesarean section. In the exposed/methyldopa cohort, the risk of preterm birth was significantly higher than the control (27% vs 10%; adjusted odds ratio, 4.11; 95% CI, 2.4–7.1) [23C]. The results of this study should be interpreted with caution due to the small sample size [23C]. Furthermore, the lack of comparison to women with untreated hypertension makes it difficult to determine if the adverse effects seen are due to methyldopa treatment or the disease itself [23C].

Renin–Angiotensin System Blockers

The 2009 analysis of NBDPS data showed an increase risk of Ebstein malformation with use of any renin–angiotensin system blocker (OR 26.4; 95% CI, 2.3–306) with first trimester exposure [19C]. The 2017 NBDPS analysis showed renin–angiotensin system blockers were associated with an increased risk of PVS (aOR, 3.74; 95% CI, 1.39–10.17), VSD-PM (aOR, 6.58; 95% CI, 1.55–27.97), and ASD2 (aOR, 3.25; 95% CI, 1.29–8.20, respectively) [20C].

Diuretics

The 2009 analysis of NBDPS data showed an increase risk of septal defects with use of any diuretic in the first trimester (OR 13.2; 95% CI, 1.1–692) [19C]. The 2017 NBDPS analysis showed diuretics were associated with an increased risk of ASD2 (OR 3.22; 95% CI, 1.30–7.99) [20C].

Calcium Channel Blockers

A 27-year-old woman was diagnosed with gingival hyperplasia after taking nifedipine for 9 weeks [24A]. This diagnosis was made during a hospital visit for preeclampsia [24A]. Upon presentation, nifedipine was discontinued and the patient was started on methyldopa for her hypertension [24A]. After about 48 h, the gingival hyperplasia seemed to be resolving [24A]. She successfully gave birth 2 weeks later with a complete resolution of her gingival hyperplasia [24A]. Likelihood that the gingival hyperplasia was caused by nifedipine was confirmed with a Naranjo score [24A]. Neither the 2009 nor the 2011 NBDPS found any specific association with calcium channel blocker association and congenital heart defects [19C, 20C].

PSYCHOTROPIC DRUGS

Antidepressants

Based on US studies, it is estimated that nearly 10% of pregnant women fill antidepressant prescriptions during gestation [25R, 26R]. The use of any antidepressant

increases the risk of hypertension or preeclampsia up to 1.5-fold [27MC, 28C]. The risk is directly correlated to duration of exposure, with a higher relative risk when prescribed for 4 or more months vs 2 months or less (1.47 and 1.05, respectively) [29MC]. The association with dose is unclear.

All antidepressants are associated with neonatal adaptation syndrome (NAS) shortly after birth [30MC, 31R, 32R, 33M, 34R]. These symptoms are usually mild, last several days, and may include respiratory complications, irritability, tremor, increased crying, hypo- or hypertonia and hyperreflexia [34R]. Of the serotonin reuptake inhibitors (SRIs), NAS has been documented in up to 30% of infants [34R, 35R], and is most commonly seen with paroxetine or venlafaxine [31R].

Bupropion

The lack of serotonergic effect of bupropion is attractive, as alterations in serotonin are potentially linked to fetal development abnormalities [36C, 37R]. In addition, the benefit of bupropion as a smoking cessation agent adds to its appeal [36C].

General Malformations and Risks

General malformation risks, as well as miscarriage or fetal demise, appear to be low with bupropion. Birth defect rates are approximately 3.6%, which is similar to the general population [36C]. The Bupropion Pregnancy Registry assessed pregnant women maintained on bupropion between 1997 and 2008, and found no increase in spontaneous miscarriage [38S]. A small prospective study, though, found an increase in miscarriage in bupropion-exposed mothers compared to controls (14.7% vs 4.5%, $P=0.009$) [39C]. However, this is within the general population miscarriage rate (14%–22%) [40R], however, several additional studies found no significant difference, or a lower risk, for premature birth and lower gestational weight at birth compared to controls [39C, 41MC].

Cardiovascular

Cardiac malformations are frequently associated with bupropion, but the data are inconclusive [31R]. A case–control study assessing first-trimester exposure of bupropion found an adjusted odds ratio of 1.6 (95% CI 1.0–2.8) for ventricular septal defect with any bupropion use. In women exposed only to bupropion and no other antidepressants, the risk was slightly higher (aOR 2.5, 1.3–5.0). No increased risk of left sided defects was found [42MC].

Mirtazapine

Mirtazapine has the benefit of replacing benzodiazepines and sedative hypnotics for the treatment of insomnia and other sleep disorders that may occur during pregnancy. This is to avoid the concerns with benzodiazepine-like drugs such as dependency, neonatal withdrawal and 'floppy baby syndrome' [33M]. In addition, its antiemetic and antinausea properties makes it attractive for women with depression and significant morning sickness. While only case reports are available regarding the use for pregnancy-related nausea and vomiting, it appears to be effective [43c].

General Malformations

Use of mirtazapine and serotonin and norepinephrine reuptake inhibitors (SNRIs) had a higher risk of preterm birth in over 700 women, with an odds ratio of 1.60 (95% CI 1.19–2.15). No increased risk for low birth weight, intrauterine death or infant death was identified [44M]. A prospective study in 104 women found a statistically significant increase in preterm birth with mirtazapine vs known non-teratogenic drugs ($P=0.04$). However, there was no difference compared to other antidepressants ($P=0.61$). There was also no difference in fetal demise, gestational age at birth or birth weight [33M, 45C]. Overall, three studies ($N=266$) reported a higher risk of preterm birth after mirtazapine exposure [44M, 45C, 46c]. However, multiple confounders were uncontrolled such as concomitant drugs, gestational or maternal age, smoking or alcohol use, and severity of depression.

Over 300 cases have been reported with no increased risk of major malformations compared to antidepressants or known non-teratogenic drugs [33M, 44M, 45C, 47c, 48C]. However, there may be risks that have been undetected due to the limited number of cases.

Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs)

Congenital Malformations

A systematic review found relative risks for major congenital malformations with first-trimester use of venlafaxine of 1.12 (95% CI 0.92–1.35), and 0.80 (0.46–1.29) for duloxetine. This is approximately a major malformation rate of 3.36% and 2.40%, respectively, and is comparable to the background rate [49M]. Additional studies have not found an increase in major malformations with duloxetine ($P=0.99$) [50C, 51C]. A possible increase in spontaneous abortion has been reported, but with several confounding factors such as depression itself and concurrent drugs [52R].

Maternal Risks

As SNRIs increase norepinephrine availability, gestational hypertension and preeclampsia are expected risks. The estimated aRR for SNRIs is 0.75 for gestational hypertension, and between 1.49 and 1.95 for preeclampsia

[53M]. There may be a higher risk for preeclampsia with venlafaxine over duloxetine (aRR 1.57 vs 0.89, respectively) [31R, 54MC]. Blood pressure should be monitored regularly. Data remain limited, especially with the newer SNRIs such as desvenlafaxine or levomilnacipran, and additional studies are needed.

Selective Serotonin Reuptake Inhibitors (SSRIs)

Infants exposed to any SRIs such as SSRIs or SNRIs have higher rates of preterm birth, lower birth weight, and respiratory problems than the general population [30MC, 35R].

Major Malformations

Rates for major malformations with SSRIs are within the background rate of approximately 3% [35R]. However, fluoxetine is associated with higher rates (OR 1.14, CI 1.01–1.30) [55R]. For this reason, and its prolonged half-life, fluoxetine is recommended to use with caution.

CARDIOVASCULAR

All SSRIs are associated with a modest increase in congenital cardiac abnormalities, but paroxetine has the highest risk (OR 1.44, CI 1.12–1.86) [31R, 55R]. Paroxetine is a pregnancy category D and is not recommended during pregnancy.

Respiratory

Persistent pulmonary hypertension of the neonate (PPHN) is associated with SSRI use [56R]. Most respiratory issues are mild, requiring only temporary supportive care. Regardless, there is a statistically significant increase in PPHN with SSRIs, with the highest risk during the second-trimester (OR up to 4.28) [56R, 57MC].

Neurocognitive

A large cohort study reported an adjusted hazard ratio for autism spectrum disorder (ASD) of 1.59 (95% CI 1.17–3.17) with exposure to any serotonergic antidepressant. However, significance was lost after controlling for confounding factors (HR 1.61, CI 0.997–2.59) [58MC]. With SSRIs specifically, a meta-analysis identified an odds ratio of 1.45 (95% CI 1.15–1.82). Significance was lost after comparing to women with untreated psychiatric disorders (OR 0.96, CI 0.57–1.63). The authors concluded that there may be an increased risk with antidepressant exposure, but maternal diagnoses may be a confounder [59M]. Despite significant overlap in included studies, a second systematic review and meta-analysis found an association between any prenatal SSRI exposure and ASD (OR 1.82, CI 1.59–2.10, $P = 0.00$) [60M]. The true correlation of ASD with antidepressants and maternal mental health is unclear, but should not prevent treatment [61MC].

Maternal Risks

Postpartum hemorrhage is a known risk with SSRIs [31R], with the highest risk during late pregnancy (RR 1.53, 95% CI 1.25–1.86) [34R]. Gestational hypertension is also associated with SSRIs, especially sertraline, paroxetine and fluvoxamine [28C, 30MC]. If left uncontrolled, this may progress into preeclampsia. The adjusted relative risk (aRR) for preeclampsia with SSRIs is between 1.05 and 3.16 [53M]. Regardless of the antidepressant, there is a higher risk of hypertension and preeclampsia when prescribed after 12 weeks of gestation [53M].

Dose Adjustment

It is often recommended to taper the dose potentially to discontinuation during the third trimester, and resume after birth [34R]. However, due to pharmacokinetic changes during pregnancy, SSRIs may require dose increases to maintain adequate concentrations [55R]. If a dose is reduced, close monitoring for psychiatric decompensation is required.

Tricyclic Antidepressants (TCAs)

General Malformations and Serious Risks

While TCAs were originally associated with cleft palate, diaphragmatic hernia and limb abnormalities, recent studies show the risk is much lower than believed [37R]. The large European study found women on TCAs had similar rates of spontaneous abortion and late fetal deaths to the general population, and 97% of infants had no congenital defects [37R]. The American Psychiatric Association (APA) and ACOG have stated they believe there is no association with TCAs and teratogenicity [37R].

However, the data are mixed. A Quebec study assessing first-trimester exposure of antidepressants in nearly 400 women found that infants exposed to amitriptyline had higher rates of ear, eye and neck malformations (aOR 2.45, 95% CI 1.05–5.72), and digestive system abnormalities (aOR 2.55, 95% CI 1.40–4.66) compared to other agents [62MC]. Other studies have estimated the risk for congenital defects to be similar to SSRIs (RR 0.9, 95% CI 0.6–1.2 vs 0.9, CI 0.7–1.2) [37R].

Neurocognitive

There may be a correlation between TCA use and ASD. A Swedish cohort study found that, after controlling for maternal depression, prenatal TCA exposure was statistically significantly associated with ASD (aOR 2.69, 1.04–6.96) [63MC]. However, a more recent Canadian

cohort study did not find any statistical correlation (aOR 1.03, CI 0.23–4.61) [64R].

Maternal Risks

TCAs also have a risk for hypertension and preeclampsia. The adjusted relative risk for TCAs is often reported as 1.10 for hypertension, and between 0.35 and 3.23 for preeclampsia [53M]. However, one study showed a decreased risk when TCAs were used in comparison to other antidepressants [29MC]. Blood pressure should be regularly monitored.

Antiepileptics and Mood Stabilizers

Carbamazepine

MAJOR MALFORMATIONS

Carbamazepine is associated with multiple malformations including neural tube defects, microcephaly, skeletal abnormalities and reduced growth rate [37R, 64R]. Major anomalies were identified 6.7% of mothers prescribed carbamazepine vs 2.5% of controls or untreated epilepsy [65M]. This is approximately twice the general population rate and was confirmed in a 2016 cohort study [66C]. Spina bifida (OR 3.6, 95% CI 1.1–4.5) and cleft palate (OR 2.4, CI 1.1–4.5) are also reported risks with carbamazepine [67M]. All risks appear to be dose related, with higher rates with daily doses greater than 1000 mg [68MC].

Divalproex Sodium

MAJOR MALFORMATIONS

When taken during the first trimester, there is a 20-fold risk for neural tube defects, cardiovascular abnormalities, developmental delay, and endocrine disorders compared to the general population [37R, 69R]. Highest risks are with daily doses greater than 1100 mg compared to other AEDs (OR 7.3, $P < 0.0001$) [70C].

An ongoing case–control study assessed first-trimester AED exposure and found a higher risk of congenital malformations with divalproex, including neural tube defects (aOR 9.8, 95% CI 3.4–27.5), oral cleft (aOR 4.4, 1.6–12.2), heart defects (aOR 2.0, 0.78–5.3) and hypospadias (aOR 2.4, 0.62–9.0) [71MC]. Other defects found statistically more frequently than other AEDs included skeletal defects and genitourinary malformations [68MC].

Children exposed to divalproex during the first 3 months of gestation may experience fetal valproate syndrome (FVS). Some common features include facial deformities including connecting epicanthal folds, flat nasal bridge, small nose, anteverted nostrils, shallow philtrum, and small mouth with downturned angles, thin upper vermilion border, as well as delayed neurological development, microcephaly and other skeletal or muscular abnormalities [72c]. Sufficient folic acid should be given while taking divalproex to prevent neural tube defects [72c].

NEUROCOGNITIVE

Developmental delay and ASD are seen with divalproex. Developmental delay is associated with lower daily doses than other malformations (greater than 800 mg) [73C, 74C, 75C]. ASD has been identified up to 10 times more frequently in those exposed to divalproex than the general population [37R].

LAMOTRIGINE

Most studies of in utero exposure have not found increased malformations rates with lamotrigine [37R, 64R]. In addition, there are no cases of developmental delay with lamotrigine use up to 6 years of age [76C, 77R].

However, lamotrigine doses must be increased during pregnancy due to estrogen level changes. In epilepsy, doses must be increased by an average of 250% [69R, 77R, 78c]. While doses are lower in mood disorders, patients should be closely monitored for destabilization of symptoms during the third trimester, and doses may need to be increased.

Lithium

GENERAL RISKS

Lithium freely crosses the placenta, so fetal and maternal blood levels are equivalent [37R]. Despite this, significant fetal toxicity is relatively limited. Reported symptoms include lower Apgar score at birth, hypotonicity, lethargy, goiter, increased birth weight, fetal heart failure and diabetes insipidus [37R, 64R].

The reported risks with lithium appear to be dose related. A small study of 20 infants compared high (>0.64 mEq/L) vs low exposure (<0.64 mEq/L), and found infants exposed to high concentrations had significantly lower Apgar scores, more days in the hospital, lower birth weight and were more likely to be born prematurely (all $P < 0.05$). In addition, over twice as many high concentration infants had cardiac complications [79c].

EPSTEIN'S ANOMALY

A 1976 study found a 10-fold increased rate of Epstein's anomaly than the general population [80C]. More recent studies indicate a lower risk than originally believed, but higher than the general population [37R, 74C, 81M]. A fetal echocardiogram may be indicated at 16–20 weeks [37R, 69R].

Antipsychotics

MAJOR MALFORMATIONS

Umbilical cord to maternal plasma ratios range between 25% and 70% for first-generation antipsychotics (FGAs)

and second-generation antipsychotics (SGAs) [37R]. Of these, olanzapine has the highest ratio, but has little data demonstrating major congenital malformations [37R, 82M, 83M].

Some of the FGAs, namely, phenothiazines such as perphenazine, have no identifiable teratogenicity. A prospective cohort study of over 1300 pregnancies taking FGAs showed no increase in congenital abnormalities or death [37R, 84MC]. A large national registry did not find an increased risk in congenital defects with FGA or SGA use [85MC, 86C]. Another study of over 400 women found a nonsignificant increase in malformations in women prescribed SGAs vs those who stopped before pregnancy, or controls [87MC]. However, meta-analyses have found a more than twofold increased odds in congenital and cardiac malformations with antipsychotic use [88M, 89M]. Risperidone may have a slightly higher comparative risk for major malformations (RR 1.26, CI 1.02–1.56), especially cardiac (1.26, CI 0.88–1.81) [85MC].

STILLBIRTH OR ABORTION

Stillbirth or spontaneous abortion are reported with SGAs, but the data are conflicting [82M, 89M]. The lowest risk agents are quetiapine and olanzapine. However, these have the highest risk for gestational diabetes which is associated with other pregnancy complications [90R, 91C].

NEUROCOGNITIVE

There may be a risk of neurodevelopmental delay or behavioral disorders with in utero antipsychotic exposure, but data are limited [87MC]. Infants exposed to SGAs showed delayed cognitive, motor, social and emotional functioning development, and adaptive behavior at 2 months old vs unexposed infants ($P < 0.01$ for all) [92c]. By 6 or 12 months, there were no significant differences [92c].

Clozapine may be the highest risk agent for developmental delay. Infants exposed to clozapine had additional signs of developmental delay at 2 and 6 months vs olanzapine, quetiapine or risperidone. Despite no significant difference at 12 months, clozapine should be limited to treatment-refractory patients [93c].

WITHDRAWAL

NAS is a risk after antipsychotic exposure. A prospective cohort study found SGA withdrawal syndromes occurred in 15% of cases, most frequently with quetiapine and olanzapine [94C]. However, most women were taking multiple psychotropic agents, so causality is difficult to assess [94C]. The most frequent symptoms include agitation, tremors, abnormal muscle tone, sleeping or feeding difficulties and respiratory complications [95R]. Matched cohort analyses have determined the risk for serious symptoms is small [96MC].

DOSE ADJUSTMENT

Serum concentrations are significantly lower during the third trimester for quetiapine (−76%, CI −83%, −66%; $P < 0.001$) and aripiprazole (−52%, CI −62%, −39%; $P < 0.001$), but not for olanzapine ($P = 0.40$) [97C]. This may be related to a decrease in plasma proteins [97C]. In addition, several P450 enzymes are induced during pregnancy such as CYP3A4. This may affect antipsychotics, but no definitive studies have been completed [82M, 97C].

Readers are also referred to the review published on the related topic [98R].

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Further Reading

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