Adverse drug reactions and adverse drug events associated with use of psychotropic, antiepileptic, antihypertensive and antidiabetic drugs in pregnancy

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PSYCHIATRIC DRUGS

Antidepressants

Although over 20% of women will experience depression during pregnancy (antenatal) or within 12 months of giving birth (postpartum), less than 15% of these women will receive treatment [2R]. Untreated antenatal depression has significant consequences for both the mother and fetus [1R]. Unmanaged postpartum symptoms lead to lactation issues, disrupted maternal-infant bonding, maternal suicide or infanticide, and may impact emotional and mental development of child through school-age [2R]. Most prescribers recommend continuing pharmacotherapy that was effective during previous episodes (if known) and using the lowest effective dose [2R]. However, some antidepressants require dose increases during the third trimester due to increased volume of distribution and CYP450 induction and may be inappropriately dosed during pregnancy [2R]. There may also be pharmacogenetic risks, with some serotonin transporter genotypes being associated with adverse neonatal effects when exposed to selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) during gestation [3R]. In spite of these potential effects, there are no pharmacogenetic dosing recommendations specific to pregnancy.

The studies regarding psychotropic medications during and after pregnancy are confounded by numerous factors including psychiatric diagnoses themselves, antenatal substance use, and socioeconomic factors, and available psychiatric guidelines often contradict one another [2R]. Another factor is that women able to participate in prospective clinical trials frequently have less severe symptoms, and higher socioeconomic standings [2R]. In addition, observational trials comparing those who continue medications during pregnancy vs those who discontinue have shown that those who continue often have more severe symptoms which may impact findings [2R].

Overall, antidepressants have several risks including altered neonatal growth such as an increased placental

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weight to birth weight (PBW) ratio. Infants with an increased PBW are associated with increased risk of hypertension and cardiovascular death, as well as some psychiatric diagnoses especially in males [4c]. Frayne and colleagues found an increased PBW ratio for women taking antidepressants alone ($n=50$), or in combination with second-generation antipsychotics ($n=59$) vs those unexposed ($n=58$) or taking second-generation antipsychotics alone ($n=75$) [4c]. An elevated ratio may, therefore, indicate poor neonatal development or poor placental efficiency when antidepressants are used and should be investigated further.

Neonatal withdrawal, or poor neonatal adaptation syndrome (PNAS) has been identified with nearly all psychotropic drugs [2R]. Previous recommendations included tapering medications during third trimester to avoid PNAS, but this is not advised due to risk of psychiatric decompensation, and no demonstrated improvement in neonatal outcomes [2R].

Bupropion

While cardiovascular abnormalities have been reported with bupropion use, the validity of these reports remains unknown [1R]. A recent meta-analysis assessed smoking cessation in pregnant women found the pooled estimate of major congenital malformations (MCMs) among live-born infants was 1% (95% CI 0%–3%) but with high heterogeneity ($I^2=80.9\%$) [5M]. There was no evidence of low birth weight or premature birth in this study, but the authors conclude additional, larger studies are needed to confirm this [5M].

Mirtazapine

General malformations and risks

Mirtazapine appears to be one of the safer antidepressants in studies as no increased risk of MCM have been identified to date [2R]. However, data remain limited.

Selective serotonin reuptake inhibitors (SSRIs)

General malformations and risks

Although MCMs, particularly cardiac abnormalities, have been identified with the use of paroxetine [1R], the reported data remain conflicted regarding the impact of maternal psychiatric diagnosis with subsequent medication administration. In a large meta-analysis of over 9 million infants with first trimester exposure to SSRIs, there was an increased risk of MCMs (RR 1.11, 95% CI 1.03–1.19) and congenital heart defects (CHD) (RR 1.24, 95% CI 1.11–1.37) associated with paroxetine exposure (doses were not specified). However, this significance was lost when only including women with psychiatric diagnoses (RR 1.04, 0.95–1.13 and RR 1.06, 0.90–1.26, respectively) [6M]. Other meta-analyses have also confirmed that paroxetine was associated with MCMs (RR 1.18, 1.05–1.32), although doses were not specified. This meta-analysis also showed that fluoxetine was associated with both MCMs (RR 1.20, 1.07–1.28) and CHD (RR 1.24, 1.02–1.51) (unspecified doses). Surprisingly, the first study also found an increased risk of both MCMs (RR 1.20, 1.09–1.31) and CHD (RR 1.30, 1.12–1.53) with citalopram exposure (unspecified doses). As with paroxetine, the significance was lost when including only women with psychiatric diagnoses [6M].

SSRIs are linked to suboptimal fetal growth [1R]. A recent meta-analysis demonstrated an increased risk for small for gestational age (pooled RR 1.45, 95% CI 1.18–1.76, $P=0.001$) with moderate heterogeneity ($I^2=66\%$). Low birth weight was still significant with SSRI use if only high-quality studies were included (OR 1.35, 95% CI 1.243–1.467, $P=0.00$) [7M]. The pathophysiology is unknown but may be related to fetal inability to metabolize SSRIs and resulting accumulation of serotonin. Prospective well-controlled trials are needed to confirm this association.

There are also maternal complications with antenatal SSRI use including gestational hypertension and preeclampsia. Since gestational hypertension increases the risk of developing preeclampsia during late pregnancy, most research has focused on this effect. A retrospective cohort study including 539 women exposed to any antidepressant (TCAs, SSRIs, MAOIs, moclobemide, SNRIs, bupropion, mirtazapine, trazodone or nefazodone) during the first two trimesters (over 70% to SSRIs and nearly 17% to TCAs) found increased odds of developing gestational hypertension with antidepressant exposure after controlling for several confounders such as concomitant medications or mean maternal age at delivery (aOR 2.00, 95% CI 1.28–3.13). Use of SSRIs monotherapy also posed an elevated risk (aOR 2.07, 95% CI 1.25–3.44). The study population was identified from the Netherlands "pregnancy database" from 1994 to 2016, including nearly 600 000 patients [8C]. Post-hoc analyses identified that the risk was only seen in women exposed to more than 30 defined daily doses (DDD) of SSRI treatment during the study period [$\geq$30 DDD aOR 2.27 (95% CI 1.44–3.60) vs $\leq$30 DDD aOR 1.28 (0.56–2.92, $P=0.561$)]. Women who discontinued treatment during the first 10 weeks of gestation had no increased risk ($P=0.205$), while the odds increased with longer exposures; an exposure through 20 weeks had aOR 2.66 (1.35–4.12) [8C]. Providers should discuss and monitor for risk of gestational hypertension for patients taking SSRIs during pregnancy.

PNAS also occurs with gestational SSRI exposure. This condition may impact up to 30% of infants exposed to SSRIs, but is usually mild and resolves within 48 h [2R].

Respiratory

Persistent pulmonary hypertension in the newborn (PPHN) is slightly increased with SSRI use (within FDA approved doses for treatment of major depressive disorder) when compared to the general population (adjusted OR 1.28 vs 1.14 in a study of over 3 million women) [2R]. Both SSRI and serotonin-norepinephrine reuptake inhibitor (SNRI) use during any trimester in over 150 000 women was associated with a risk of PPHN (aOR 2.42, 95% CI 1.68–3.48) with moderate heterogeneity ($I^2 = 69\%$), although doses were not specified. Of the SSRIs, the risk appears lowest with sertraline and highest for fluoxetine, but this association requires additional confirmation [9M]. The overall incidence is low (an increase of 1.1 out of 1000 live births) but the possibility of adverse fetal effects should be discussed with patients before continuing SSRIs [9M].

Neurocognitive

The debate of autism spectrum disorder (ASD) due to use of psychotropics is ongoing. After adjusting for risk of maternal depression and other potential confounders, significance has been lost in previous SSRI trials (doses within normal FDA approved ranges for treatment of major depressive disorder) [1R,2R].

While there has been no identified impact of SSRI use on IQ or mental indices up to 1 year of life [2R], possible impacts later in life, such as in preschool and adolescence, have been of special interest. In a Norwegian cohort study including 4000 children up to age five, there was an increased risk of anxious or depressed behaviors in children exposed to SSRIs (ATC group N06AB) during the third trimester (adjusted beta 0.50, 95% CI 0.04–0.96). Early exposure (in the first and second trimesters) was not statistically significant [10MC]. It should be noted that this study had multiple uncontrolled confounders such as disease severity, and unknown compliance and dosages. Another study evaluating 139 children (51 exposed to SSRIs during gestation) found that SSRI exposure was not associated with decreased executive functioning as rated by the mothers by age 6 years. However, more severe maternal depressive symptoms at an earlier age (3 years old) was associated with poorer child executive functioning later in life (6 years old) [11c]. The authors caution that this is a small trial, and there may be unidentified neurocognitive impact seen later in development. Medication name and doses were not included and should be considered as a limitation. Another smaller study found similar results: no association with delayed neurodevelopment was detected in 113 women exposed to antidepressants including SSRIs (did not specify which were included) or bupropion, after controlling for pre- and post-natal depressive symptoms [12C]. However, doses were not specified.

A randomized, placebo-controlled trial assessing cognitive development up to 2 years of age in children exposed to SSRIs during gestation is underway. It will not only assess neurocognitive effects, but also evaluate impact of cognitive behavioral therapy (CBT) on antenatal depression, identify risk of negative outcomes such as preeclampsia and PNAS, and explore the impact of pharmacokinetic/pharmacogenomic differences [13S].

Tricyclic antidepressants (TCAs)

A large retrospective cohort study of 539 women exposed to antidepressants (over 15% to either amitriptyline, clomipramine, imipramine, nortriptyline, dosulepin, trimipramine, maprotiline or doxepin) found a non-significant increased odds of gestational hypertension in TCA users vs unexposed women (aOR 1.60, 95% CI 0.50–5.09, $P = 0.429$) [8C]. Doses were not specified.

Mood stabilizers

Untreated bipolar disorder during pregnancy is associated with negative maternal and neonatal outcomes such as preterm birth, fetal distress, high risk behaviors and decreased prenatal care [14R]. While drugs for bipolar carry risks, discontinuation of treatment before or during pregnancy is associated with a 70% risk of a new episode during the first trimester [14R].

Due to CYP450 3A4, 2C9 and 2D6 induction during pregnancy, as well as increased glomerular filtration rate (GFR), plasma volume and total body water, some mood stabilizers may require dose increases. While some encourage frequent therapeutic monitoring, as often as weekly [14R,15R] but the data to support this are limited. A recent randomized trial assessed the impact of antiepileptic monitoring on maternal and neonatal outcomes. A study of 267 women with epilepsy assessed the difference between adjusting antiepileptics only when clinically indicated or assessing therapy doses based on monthly serum concentrations. The authors found no difference in complications, breastfeeding difficulties, birthweight, quality of life or cord pH. In addition, there was no change in number of seizures between drug regimens (OR 0.93, 95% CI 0.56–1.50) [16C]. Providers should clinically evaluate patient's stability and disease severity before empirically adjusting doses during pregnancy or requiring more frequent monitoring.

Carbamazepine and oxcarbazepine

General malformations and risks

Carbamazepine is known to cause several malformations such as hypoplasia, craniofacial malformations, and developmental delays [1R,14R]. Tomson and

colleagues found a significant dose correlation of MCMs with carbamazepine doses over 700 mg/day (aOR 2.68, 95% CI 1.71–4.19, $P=0.0002$) [17MC]. At the same time, even low-doses (≤700 mg/day) resulted in higher odds of MCM than low-dose lamotrigine (<325 mg/day) (aOR 1.71, 95% CI 1.01–2.80, $P=0.0143$) [17MC]. Neurocognitive impacts are not well understood and the current studies are inconclusive [14R].

Oxcarbazepine may be less teratogenic than carbamazepine but the available data are limited [14R]. In a large trial of over 7000 births, maternal treatment with oxcarbazepine resulted in a similar rate of MCM to the general population [2.8% of pregnancies (10/333)] [17MC]. No significant neurocognitive impact has been found but the number of exposed cases is small [18MC]. However, doses were not reported for either meta-analysis.

Divalproex sodium

General malformations and risks

Monotherapy divalproex sodium (VPA) given during the first trimester is associated with a significantly increased risk of fetal loss (OR 1.83, 95% CI 1.04–3.45) [19M]. However, doses were not specified. When comparing combinations of antiepileptic drugs in 1688 pregnancies, combinations with VPA (712 ± 325 mg/day) were associated with higher risk of MCMs vs other combinations (RR 12.7, 95% CI 1.64–97.55). Other medications included carbamazepine, benzodiazepines such as clobazam, levetiracetam, lamotrigine, oxcarbazepine, phenytoin and phenobarbital. Serum levels were not specified [20C].

A dose association has been identified for MCMs at all doses of VPA [20C,17MC]. The highest risk is seen with daily doses over 1450 mg but low doses (<400 mg/day) also had a higher risk of MCM when compared to high dose lamotrigine (>325 mg/day) [17MC]. Any dose correlation should be interpreted with caution due to potential confounding seizure disorder severity.

Neurocognitive

Fetal valproate syndrome (FVS) is a known complication of VPA use during pregnancy, and impact on IQ/academic performance has previous been explored [1R]. A trial including over 470 000 children in Denmark found that those exposed to VPA monotherapy performed significantly worse on standardized tests than unexposed children (crude difference −0.41, 95% CI −0.57 to −0.25, $P<0.001$) [18MC]. This association remained significant after adjusting for socioeconomic factors and when compared to lamotrigine monotherapy, children exposed to VPA during pregnancy still performed significantly worse ($P=0.02$) [18MC]. After excluding children with identifiable MCMs, children exposed to VPA still performed worse than unexposed or lamotrigine-exposed children [18MC]. This study excluded all private school students and may have excluded students with special education needs which may have impacted the results.

Autism spectrum disorder (ASD) has also been associated with fetal exposure to VPA [1R]. Several recent animal studies found an increase in autism-like behaviors when VPA was administered to mice between day 12 and 13 of pregnancy [21E,22E,23E]. While the pathophysiology remains unknown, it may be associated with an increase in microRNA expression, resulting in an altered regulation of proteins [21E,22E,23E]. The gut-brain axis may also be affected as there is evidence of altered microbiome in rat models of VPA-induced ASD with an increase in enteric bacteria such as Clostridia and a decrease in gut microbiota richness as seen in children with ASD [24E].

Lamotrigine

Published data indicate no increase in MCMs compared to the general population with any dose of lamotrigine (2.9% of 2514 pregnancies vs 2.6% unexposed) [17MC,20C,25c] and limited or no effect on infant IQ or neurodevelopment up to age 12 [2R,14R,18MC,25c]. In a small study ($n=47$) of children ages 6–12, children who were not exposed to lamotrigine had more speech delay than lamotrigine-exposed children (7.2% lamotrigine vs 18% unexposed, $P=0.036$) [25c].

Levetiracetam

The EURAP registry of 7355 pregnancies (nearly 600 to levetiracetam), and the Kerala Registry of Epilepsy and Pregnancy including 1688 pregnancies (over 40 exposed to levetiracetam) including patients with seizure disorders found no increased risk with any levetiracetam use (2.8% vs 2.6% general population) [20C,17MC].

Lithium

General malformations and risks

The precise risk of malformations with maternal use of lithium continues to be debated. Many of the reported risks such as neonatal hypothyroidism, diabetes insipidus and neuromuscular complications appear to be limited and resolve rapidly [14R,26M]. Munk-Olsen and colleagues found that malformations occurred in 7.2% of pregnancies exposed to lithium vs 4.3% in unexposed (aOR 1.71, 95% CI 1.07–2.72) with no significant risk of major cardiac malformations due to administration of any drug [27M]. This study included patients from three population-level register-based cohorts in Denmark, Sweden and Canada, and three clinical cohorts from

the Netherlands, United Kingdom and United States. Women were included if there were at least two dispenses of lithium during the pregnancy, and no doses were excluded. A study of over 700 lithium-exposed pregnancies showed an increased risk of neonatal admission to the special care baby unit within the first month of life (aOR 1.62, 95% CI 1.12–2.23). However, there was no drug-related association with preeclampsia, gestational diabetes, fetal distress, postpartum hemorrhage, preterm birth, low birth weight or small for gestational age [27M].

Cardiac

Recent data continue to demonstrate a lower risk for Ebstein's anomaly than originally reported [1R,15R]. A meta-analysis of 727 women with 51 infant malformations had no cases of Ebstein's anomaly [27M]. This study included patients from three population-level register-based cohorts in Denmark, Sweden and Canada, and three clinical cohorts from the Netherlands, United Kingdom and United States. Women were included if there were at least two dispenses of lithium during the pregnancy, and no doses were excluded.

Neurocognitive

A recent meta-analysis including three cohort studies found no difference in IQ score or overall intelligence tests in children up to age 15. Overall, the three cohort studies included 154 patients included 57 controls. Mean dose of lithium was reported for only one study (927 mg) with a follow-up time ranging from 1 to 15 years. Parent-reported developmental questionnaires were used in two studies, while a telephone interview to determine developmental delay was used for the third [26M]. Poels and colleagues also included four case reports documenting normalization of any neurodevelopmental deficits seen in infants. The infants were evaluated up to month 13, and doses were not specified [26M]. The authors caution that there is a paucity of available data, and high-quality studies are needed.

Dosing considerations

Most sources recommend targeting 0.6–1.0 mEq/L or the lowest effective serum level when administering lithium twice daily to avoid high peak concentrations and to have increased frequency of monitoring during the third trimester [14R]. In addition, a fetal echocardiography and level 2 ultrasound should be completed around 16 weeks for all infants exposed during the first trimester [14R].

Antipsychotics

General malformations and risks

Most second-generation antipsychotics (SGAs) have not been associated with major malformations, except for risperidone (cardiac) [1R,14R,28R]. A recent report of over 150 infants exposed to quetiapine during gestation found a non-significant unadjusted OR for MCMs (0.90, 95% CI 0.15–5.46, $P=0.91$). This study included all women enrolled in the National Pregnancy Registry for Atypical Antipsychotics at Massachusetts General Hospital with any first-trimester exposure to quetiapine (doses unspecified) [29C]. It should be noted that this trial was small and requires confirmation. Neonatal outcomes have not differed in significance in studies that control for maternal psychiatric diagnosis [14R].

Metabolic syndrome such as obesity and gestational diabetes (GDM) is a concern with the use of SGAs, particularly with high metabolic risk agents like olanzapine or quetiapine [14R]. During an evaluation of 1.5 million pregnant women enrolled in the Medicaid database, an increased risk of developing GDM with treatment with either olanzapine or quetiapine was found (aRR 1.61, 95% CI 1.13–2.29; (aRR 1.29, 1.01–1.62, respectively) but not with aripiprazole, ziprasidone or risperidone. This study included all patients in a Medicaid claims database with filled a prescription for one of the studied antipsychotics (doses unspecified) 3 months before the last menstrual period [30MC]. The risk of GDM development was similar between women who continued aripiprazole or ziprasidone vs those who discontinued, though doses were unspecified [30MC]. For this reason, administration of metabolically-neutral antipsychotics such as aripiprazole, lurasidone or ziprasidone should be given during pregnancy based primarily on patient response and tolerability [14R].

It should be noted that even these 'metabolically neutral' antipsychotics have risks. Out of 26 patients in Australia, women who used aripiprazole reported gestational hypertension (15.4%) more often than the general population (3.7%) ($P=0.015$) with a dose range of 5–60 mg during the first trimester (mean 17.98 mg) [31r]. Other studies have shown aripiprazole to be associated with increased risk of premature birth (OR 2.57, 95% CI 1.06–6.27) and fetal growth retardation (OR 2.97, 1.23–7.16), but not with GDM, miscarriage or MCMs. This systematic-review included 93 studies with doses ranging from 5 mg daily to 30 mg daily when specified, and the most frequent dose reported was 10 mg [32M]. The authors concluded that most studies assessing gestational metabolic risk do not include metabolically-neutral antipsychotics and the risk could be underreported.

Neurocognitive

There are possible delays in neurocognitive, motor and emotional development during the first months of development but resolves by 1 year with any antipsychotic exposure with currently available literature [14R]. Poels and colleagues found a small increased risk of neurodevelopmental changes at age 6 months (pooled relative risk 1.97 [95% CI 1.47–2.62), $P<0.001$] in nearly 3000

children with a variety of antipsychotics including chlorpromazine, clozapine, risperidone, olanzapine, quetiapine, phenothiazines (as a class), and unspecified "antipsychotics." The doses widely varied between the studies, but were all within the FDA approved range for treatment of schizophrenia [26M]. This study, however, reported inconsistent follow-up with a poor control of confounding factors. The one-third of included studies that controlled for maternal mental illness found no significant differences in neurodevelopment by age 1 year [26M]. The data were limited to cohort studies and did not specify the generation or specific antipsychotic studied.

Withdrawal

NAS after antipsychotic treatment is well-known and well-documented [1R]. Most commonly, it occurs after third trimester exposure to any antipsychotic, and leads to a higher risk of neonatal respiratory distress, decreased muscle tone and perinatal cardiac abnormalities [32M].

Dosing considerations

As many antipsychotics are metabolized through either CYP450 2D6 or 3A4, doses may need to be increased during the second and third trimesters [14R,33c]. Patients should be closely monitored for psychiatric decompensation during these time periods, and dose increases should be considered as clinically indicated [14R].

ANTIEPILEPTIC DRUGS

Epilepsy is a chronic and often progressive neurological disorder. It affects approximately 3 million people in the United States and 65 million worldwide. About 1 in every 26 Americans will be diagnosed with epilepsy at some point in their lifetime [34E]. Antiepileptic drugs (AEDs) are chemical entities used to reduce the frequency of seizure episodes by decreasing abnormal hyperexcitability in a focal area or across both hemispheres of the brain [35R]. Having epilepsy is not an issue for the mother or child during pregnancy but the use of AEDs while pregnant have been linked to hereditary malformation and neurocognitive dysfunctions to the fetus [36C,37C]. Other obstetric effects are postpartum hemorrhage, intrauterine growth restriction, low birth weight, miscarriage and even fetal death [37C,38C].

The use of AEDs in pregnant women is often high because of their other benefits in treating mood disorders, margarines, and neuropathic pain [39r]. The North American AED Pregnancy Registry (NAAPR) and the International Registry of Antiepileptic Drugs in Pregnancy (EURAP) suggest the newer AEDs such as lamotrigine and levetiracetam have the lowest rates of major congenital malformations (2.0%–2.9% and 1.6%–2.4%, respectively). This is in contrast to the older AEDs such as sodium valproate which are reported to have the highest rates of major congenital malformations in pregnancy 9.3%–9.7% [39r].

Sodium valproate

Valproate, phenytoin, carbamazepine, primidone, phenobarbital and topiramate are considered to be older generation AEDs. According to a meta-analysis of observational data on major congenital malformations in children of mothers taking valproate only to treat epilepsy ($N=467$) vs children to mothers without epilepsy ($N=1.936$), there was a quintupled increase risk of congenital malformations ([RR]=5.69; 95% CI, 3.33–9.73). Valproate adverse effects of congenital malformations are directly proportional to the drug dose. Valproate had an even higher risk than carbamazepine ($RR=3.69$), phenobarbital ($RR=2.84$), phenytoin ($RR=2.38$) and topiramate ($RR=3.69$) [40R]. A cohort study showed that women who took valproate between 250 and 1500 mg during the first trimester of pregnancy were at a higher risk (sevenfold) of their children having congenital malformations compared to a baseline rate of 1.62% [41R].

A case report published in 2016, described a 16-month-old girl with congenital malformation presented as limited extension of fingers of both hands. She was born full-term by cesarean section. Her mother had been epileptic for 12 years and before pregnancy was taking 1.5 g of valproate daily. During pregnancy, the mother dose of valproate was reduced to 500 mg twice a day. In spite of the dose reduction, the girl had a camptodactyly deformity on her right thumb and, the third and fourth fingers [42A].

Newer antiepileptic drugs

The newer AEDs include lamotrigine, levetiracetam, and oxcarbazepine. A comparative study published in 2018, investigated the use and efficacy of lamotrigine, levetiracetam, and oxcarbazepine during pregnancy over a 12 year period [38C]. The authors compared data from two periods (June 2001 to October 2007 and January 2008 to May 15). There was a total of 240 patients includes in the study of those 127 mothers (82%) was on an AED monotherapy. The patients included in the study were those at the onset of pregnancy, at the end of the second or third trimester, post-delivery, and 1 year post-delivery. The AEDs used mainly as monotherapy were lamotrigine (37 patients, 29%), levetiracetam (25 patients, 20%), carbamazepine (24 patients, 19%), valproate (26 patients, 20.5%), oxcarbazepine (6 patients, 5%), topiramate

(5 patients, 4), and primidone (1 patient). The children with major congenital malformations (MCMs) in the lamotrigine and levetiracetam groups, the mothers were dose at 250–300 mg/day and 1000–1500 mg/day, respectively. Only two mothers out of 28 taking monotherapy levetiracetam had children with MCMs. The comparative study concluded that there was a trend in medication use with a decrease in the amounts of older AEDs (i.e. valproate, carbamazepine, phenobarbital, etc.) and a concomitant increase in the newer AEDs. For example, levetiracetam treatment was increased from 1.3% to 20% whereas carbamazeoine and vaporate were decreased from 38% to 19% and 25% to 20%, respectively. Eight children from the comparative study were reported to have one or more MCM. With the reported MCMs there was a difference in the percentage between the polymedicated and monomedicated mothers. The monotherapy patients were taking valproate, carbamazepine, lamotrigine, or levetiracetam. The polymedicated epileptic mothers were receiving either valproate and topiramate or ethosuximide and topiramate [38C].

Lamotrigine

A cohort study including 83 epileptic women who had given birth between January 2004 and August 2014 were all treated with lamotrigine during pregnancy. All newborns were evaluated post childbirth for congenital malformations, vital signs, and Finngan score. No congenital malformations were reported. There was no dose correlation with the use of lamotrigine. Based on these results, it was concluded that lamotrigine to be generally a safe AED to use during pregnancy [43c].

ANTICOAGULANT DRUGS

Warfarin, unfractionated heparin, and low molecular weight heparin

The 2012 Antithrombotic Therapy and Prevention of Thrombosis, 9th ed.: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (AT9) recommend the use of Low Molecular Weight Heparin (LMWH) over unfractionated heparin (UFH) for treatment or prevention of venous thromboembolism (VTE) [44S]. LMWH is also preferred over vitamin K antagonists (VKA) such as warfarin [44S]. For some women with antiphospholipid antibody syndrome prophylactic UFH or LMWH with aspirin is recommended [44S]. In the case of pregnant women with mechanical heart valves, AT9 recommends using any one of three anticoagulation methods: subcutaneous LMWH twice a day with the dose adjusted to the manufacturer provided peak anti-Xa LMWH level at 4 h post dose; subcutaneous UFH every 12 h with the dose adjusted to 0.35–0.7 units/mL anti-Xa heparin level or two times control aPPT at mid dose interval; or either LMWH or UFH until the 13th week followed by VKA until close to delivery when a heparin would be resumed [44S]. In women with very high risk for thromboembolism, VKA is suggested throughout pregnancy until close to delivery when a heparin will be substituted [44S]. For women with mechanical heart valves, treatment with VKA therapy during pregnancy has a lower risk of thromboembolic complications and mortality as compared with UFH or LMWH but a higher risk of spontaneous abortion and fetal complications such as bone and cartilage abnormalities that are referred to as fetal warfarin syndrome [44S,45c,46A].

A 2017 meta-analysis of seven prospective cohort studies conducted between 2000 and 2016 compared outcomes of anticoagulation therapy in women with mechanical heart valves [47M]. The study compared 583 pregnancies where pregnant women with mechanical heart valves were treated with either heparin ($n=199$) or warfarin ($n=325$) [47M]. Doses were not provided [47M]. First trimester valve thrombosis, the major cause of maternal death, was more common with heparin as compared to warfarin (OR: 14.58; 95% CI 3.94–53.94; $P<0.0001$; $I^2=0\%$) [47M]. No significant difference between the treatments was found in rates of spontaneous abortion or fetal loss after 28 weeks [47M]. Despite fetal risks, warfarin is the most effective therapy for prevention of maternal mechanical valve thrombosis in pregnancy.

One of the studies included in this meta-analysis compared outcomes of warfarin vs heparin in 49 pregnancies. The patients were divided into three groups: heparin warfarin (5 mg or less per day) or warfarin (greater than 5 mg per day) [45c,47M]. Doses of heparin were not provided [45c]. Patients only received heparin in the first trimester and all patients received warfarin from weeks 12 to 36. The heparin group had a significantly higher rate of valve thrombosis and dysfunction (45.4% vs 2.6%; $P<0.001$) [45c]. The incidence of live birth, type of delivery, spontaneous abortion, and intrauterine fetal death did not differ between the heparin and warfarin treatments [45c]. Rates of spontaneous abortion were very similar between the heparin and warfarin groups (27.3% vs 23.7%) but significantly higher in the higher vs lower dose warfarin group (77.8% vs 27.6%, $P<0.016$) [45c]. Fetal risks with warfarin use in pregnancy appear to be reduced with doses of 5 mg or less per day.

A case report described a newborn delivered by caesarean at 39 weeks gestation who was exposed to 5 mg per day of warfarin for most of the pregnancy [46A]. Warfarin therapy was interrupted from week 8 to week 10 only due to patient nonadherence. LMWH was used to bridge the patient back on to warfarin but was stopped at week 12. No dosing information was provided for

LMWH. Upon admission for the cesarean at week 39, warfarin was stopped and UFH started. No dosing information was provided for UFH. Echography at 21 weeks showed multiple dysmorphias including absence of nasal bones and malformation of lumbosacral vertebrae. A small muscular ventricular septal defect was seen on fetal echocardiogram at 28 weeks. The infant was born with nasal hypoplasia and depression of the nasal pyramid. Although warfarin given at 5 mg or less is considered less of a risk for the fetus, there remains a risk of fetal abnormalities [46A].

ANTIHYPERTENSIVE DRUGS

Current guidelines from The American College of Obstetrics and Gynecology (ACOG) recommend use of oral labetalol, nifedipine, and methyldopa as preferred agents for the treatment of chronic hypertension in pregnancy and intravenous (IV) labetalol, IV hydralazine, and oral immediate release nifedipine for acute treatment of severe hypertension [1R,48S,49S].

Intravenous labetalol vs oral nifedipine for acute severe hypertension

A recent randomized controlled trial (RCT) compared use of IV labetalol ($n=60$) and oral nifedipine ($n=60$) for treatment of acute hypertension in pregnancy [50C]. Time in minutes (min) from administration of study drug to achievement of target blood pressure of 150 mmHg systolic and/or 100 mmHg diastolic was the primary endpoint. Number of doses needed to achieve target blood pressure, maternal and perinatal outcomes, and adverse effects were secondary endpoints. Doses of labetalol were given every 15 min with an initial dose of 20 mg, then 40 mg, and then 80 mg with a maximum dose of 300 mg. Nifedipine doses were given every 15 min with an initial dose of 10 mg, then 20 mg with a maximum dose of 90 mg. There was no significant difference in rates of maternal or fetal complications. Time to achieve target blood pressure was significantly shorter for the nifedipine group (27.25 min SD 12.50 nifedipine vs 36.75 min SD 19.80 labetalol, (HR 1.821; 95% CI 1.238–2.679).Oral nifedipine treatment also achieved blood pressure control with fewer doses (nifedipine 1.82 mean doses SD 0.83 vs labetalol 2.45 mean doses SD 1.32).

Any antihypertensive drug

Data from the National Birth Defects Prevention Study (NBDPS) on small for gestational age (SGA) births were used in a retrospective cohort study (data from October 1997 to December 2011) that compared SGA ($n=1045$) births non-SGA births ($n=10\,019$) [51MC]. There was a small, but not statistically significant increase in the likelihood of antihypertensive medication exposure in the SGA births. Neither aggregate nor individual antihypertensive class exposure showed statistically significant association with SGA. Previous work by Fischer and others have shown statistically significant risk for cardiac malformation with exposure to antihypertensive medications in pregnancy [51MC,52MC,53C].

Angiotensin converting enzyme inhibitors (ACEi)

A prospective observational cohort study compared 329 ACEi-exposed pregnancies to 654 unexposed pregnancies from the German Embryotox database [54C]. The most common ACEis used were lisinopril (5 mg median daily dose, 41 exposures), enalapril (10 mg median daily dose, 68 exposures), and Ramipril (5 mg median daily dose, 175 exposures). A comparison was also made between ACEi-exposed pregnancies and methyldopa-exposed pregnancies. No dosing information was provided for methyldopa. After adjustments for covariance, there was no significant increase in rates of spontaneous abortion between the treatments. A significant increase in major birth defects was seen in the ACEi group (aOR: 2.41, 95% CI 1.07–5.43) with cardiovascular and urinary malformations being the most common [54C]. Rates of severe birth defects were not significantly different in ACEi exposed vs methyldopa-exposed pregnancies (aOR: 1.47, 95% CI 0.51–4.23).

Previous work by Hoeltzenbein and colleagues showed a higher but not statistically significant rate of spontaneous abortion with methyldopa use in the first trimester as compared with no exposure [1R,55C]. A higher but not statistically significant rate in spontaneous abortion in the ACEi group vs the methyldopa group was found (26% vs 15.2%, aHR: 1.46, 95% CI 0.84–2.55) [54C]. Similarly, the rate of major birth defects was slightly higher but not statistically significant in the ACEi group as compared to the methyldopa group (4.7% vs 3.7%, aOR 1.47, 95% CI 0.51–4.23). Women exposed to ACEi therapy early in pregnancy should be switched to a preferred agent if drug therapy is necessary but may not be at significantly higher risk of birth defects in comparison with women treated with a preferred agent such as methyldopa.

Methyldopa

A study evaluated 100 women who presented for 6 week postpartum visits at tertiary care hospital located in Mumbai [56c]. Exclusion criteria included current use of psychotropic medications, past history of psychiatric illness, and current diagnosis of psychiatric or medical

illness. The Edinburgh Postnatal Depression Scale (EPDS) was administered to each woman with 39 of 100 women showing an elevation indicative of postpartum depression. Nine women had received methyldopa during pregnancy and seven of those were found to have postpartum depression (OR 6.45 $P=0.026$). More robust prospective studies are needed to determine if this association between methyldopa and postpartum depression can be replicated.

Beta blockers

Data from the European Concerted Action on Congenital Anomalies and Twins (EUROCAT) registries were evaluated to determine whether specific congenital abnormalities were more likely with first trimester beta-blocker use [57MC]. No information on medication dose was provided. Exclusion criteria included genetic syndromes, teratogenic syndromes, skeletal dysplasia, congenital skin disorders, maternal diabetes, insulin use during pregnancy, maternal epilepsy, use of antiepileptic medications during pregnancy, and use of medication assigned FDA pregnancy category X. The final analysis included 117122 registrations from 17 different EUROCAT registries with 320 exposures to any beta-blocker. A statistically significant increase in risk for multicystic renal dysplasia (MCRD) (aOR 2.5, 95% CI 1.3–5.1, $P=0.008$) was associated with exposure to combined alpha- and beta-blockers such as labetalol (aOR 3.8, 95% CI 1.3–11.0, $P=0.012$). Further statistical analysis indicated that this association may have been a chance finding due to the small number of exposures ($n=103$). Further investigation is indicated to further evaluate this association.

ANTIDIABETIC DRUGS

Metformin, glyburide, insulin

Birth outcomes

A randomized, double-blind, placebo-controlled trial assessed the effects on maternal and infant outcomes of antenatal metformin treatment with dietary and lifestyle intervention in pregnant women who are overweight and obese [58C]. The women in this study were recruited from three public maternity units in Adelaide, SA, Australia and were randomly assigned to receive either metformin (maximum dose of 2000 mg metformin) or a matching placebo. The women received a 16-week supply of tablets and a further 12-week supply at 28 weeks gestation. Of the 524 women, 256 were in the metformin group and 258 in the placebo group. In addition, the women received an antenatal dietary and lifestyle advice from dietitians and a research scientist at different stages. The results showed no significant difference in the proportion of infants with birth weight greater than 4000 g between treatment groups. Furthermore, there was no effect of metformin on total gestational weight gain or on pregnancy and birth outcomes, maternal diet and physical activity, and maternal quality of life and emotional wellbeing. There were similar numbers of women in both treatment groups who reported experiencing nausea, diarrhea, and vomiting.

A study was conducted to compare the risks for specific birth defects between metformin-exposed diabetic women to those non-diabetic women treated with metformin for subfertility [59M]. The study population included mothers of malformed infants and nonmalformed controls with estimated due dates from 1997 to 2009 (Version 9 of National Birth Defects Prevention Study). The results have shown that when metformin was used to treat women for subfertility, most birth defects had an adjusted odds ratios that approximated the null than those diabetic metformin users.

Congenital anomalies

Previous meta-analyses studies based on small heterogeneous samples have concluded that no evidence exists to suggest a significantly high risk of congenital anomaly following exposure to metformin in humans [60M,61M]. Similarly, no epidemiological evidence from a large international population exists that rules out an overall increased risk of congenital anomalies after first trimester metformin exposure. A recent population-based exploratory case–control study investigated whether exposure to exposure to metformin during the first trimester of pregnancy increases the risk of all or specific congenital anomalies [62M]. The study used the Anatomical Therapeutic Chemical codes to identify metformin exposure and included metformin and combined metformin preparations (e.g. metformin and sulfonylurea). Using the EUROmediCAT central database, the study analyzed 50167 babies affected by congenital anomaly in Europe between 2006 and 2013. The study found that 168 babies affected by congenital anomaly were exposed to metformin (3.3 per 1000 births). The study found no evidence for of an overall increased risk of all major congenital anomalies combined after exposure to metformin during the first trimester among babies with all non-genetic anomalies combined compared with genetic controls (adjusted odds ratio 0.84, 95% confidence interval 0.55–1.30).

A retrospective population-based study using a cohort of pregnancies with diabetes across seven regions in Europe evaluated the risk of major congenital anomalies exposed to insulin analogues in the first trimester of pregnancy compared with the use of human insulin [63MC]. The study population belonged to the EUROCAT central database which holds individual standardized records of congenital anomaly registrations. These included women

with pregestational diabetes who had been referred to the hospitals and delivered between 1996 and 2012. Of the 1661 fetuses included in this study, 52.4% fetuses were exposed to human insulin only, 23.9% fetuses to insulin analogues only, and 23.7% fetuses to both human insulin and insulin analogues during the first trimester. The study revealed no increase in the risk of congenital anomalies in fetuses exposed to insulin analogues compared with those exposed to human insulin. Although two cases with severe congenital heart defects among fetuses exposed to human insulin only were found, these numbers are too small to form any conclusions.

Reproductive alterations

Metformin is widely used to treat type 2 diabetes *mellitus* and gestational diabetes. Although metformin has been considered safe, it is known to cross the placenta. A research study using Wistar female rats evaluated if maternal exposure to metformin could interfere with reproductive parameters of male offspring [64E]. The Wistar female rats in the gestational metformin group (METG) were treated with metformin 293 mg/kg/day, by gavage from gestational day 0 to gestational day 21 while the Wistar female rats in the gestational and lactational metformin (METGL) group were treated from gestational day 0 to lactation day 21. The results suggested that the sexual behavior of male offspring was affected in both metformin groups. For the METG animals, there was a significant reduction in latency to the first intromission and an increase in the numbers of intromissions until the first ejaculation. For the METGL animals, there was a significant increase in the latency to the first ejaculation in seconds and the first postejaculatory intromission. A compromised hypothalamic sexual differentiation may explain the alteration in the sexual behavior in both groups. In addition, there was a reduction in the number of spermatids, number of spermatids per organ, and daily sperm production in the METGL group.

Birth weight

While metformin is increasingly prescribed to pregnant women with polycystic ovary syndrome (PCOS), limited studies have reported the impact of intrauterine drug exposure on the future health of offspring of these women [65c,66C]. A study evaluated children ($n = 182$) of mothers with PCOS who participated in two previous randomized controlled trials of metformin use during pregnancy [67C,68c,69C]. In order to evaluate the potential of metformin to decrease pregnancy complication, the pregnant women with PCOS in both studies were randomized to either metformin (1700–2000 mg/day) or placebo from first trimester to delivery. The current study showed that the metformin-exposed children had a higher BMI at 4 years of age. Similarly, the metformin-exposed children were more overweight or obese at 4 years of age than those in the placebo group.

Macrosomia

A retrospective cohort study compared 801 gestational diabetes (GDM) women who were hyperglycemic to 1420 normoglycemic women. The results showed that women with GDM had a higher risk of preterm labor, large for gestational age, neonatal ICU admission, and neonatal hypoglycemia. The use of metformin as treatment has shown that it reduces maternal weight gain as well as the risk of macrosomia and neonatal hypoglycemia as compared to diet alone [70M].

Perinatal complications

Randomized trials have focused on comparing glyburide with insulin on maternal glycemic control as the primary outcome and not on neonatal complications of glyburide for women with gestational diabetes. A recent multi-center randomized noninferiority trial was conducted in France to compare oral glyburide vs subcutaneous insulin in prevention of perinatal complications in newborns of women with gestational diabetes [71MC]. The trial included 914 women with a singleton pregnancy and diagnosed with gestational diabetes between 24 and 34 weeks of gestation. The women were randomly assigned in a 1:1 ratio to receive glyburide (starting dosage was 2.5 mg orally once per day; the dosage could be increased if necessary every 4 days initially by 2.5 mg and thereafter by 5 mg; the increased doses were given twice daily up to a maximum of 20 mg per day) or insulin (starting dose was 4 IU given subcutaneously before meals, 1–3 times per day as necessary and increased by 2 IU every 2 days according to the postprandial blood glucose value). The results showed a higher rate of perinatal complications (including macrosomia, neonatal hypoglycemia, and hyperbilirubinemia) in the glyburide group compared to the insulin group. This difference was mainly due to an increased rate of neonatal hypoglycemia. The two groups, glyburide and insulin, did not differ in the rates of admissions to NICU.

Neonatal hypoglycemia

Hypoglycemia is a major problem in infants born following a pregnancy complicated by diabetes. In a large prospective cohort study [72C], 506 neonates were evaluated for hypoglycemia following pregnancies complicated by GDM. The neonates were born from mothers with insulin- and non-insulin-treated GDM. The study revealed high incidence of both mild (32.6%) and severe (21%) hypoglycemia, for both diet-controlled and insulin-treated GDM and across the full range of birth weight centiles.

Early onset puberty

Limited studies have evaluated the impact of GDM on adiposity and insulin resistance during adolescence, and on the onset of puberty. A recent study evaluated a large cohort of 9- to 16-year-old offspring of women with and without previous GDM and reported on their clinical and metabolic characteristics [73C]. The association of GDM between offspring puberty development was also examined. The study revealed multiple early disturbances in the cardiometabolic system in offspring of GDM pregnancies. Offspring of mothers with GDM had higher BMI and waist-to-hip ratio (WHR), higher systolic blood pressure, fasting glucose level, insulin and C-peptide levels, higher HOMA-insulin resistance. Furthermore, female offspring of mothers with GDM reached puberty earlier than control offspring. The study suggested that the offspring BMI seemed to drive the association with higher blood pressure, higher fasting C-peptide levels, adverse lipid profile, and earlier onset of puberty. Whereas the offspring of mothers with GDM still had higher WHR, fasting glucose levels, and HOMA-IR even after adjustment for both maternal and offspring BMIs.

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