**Maternal Use of Drug Substrates of Placental Transporters and the Effect of Transporter-Mediated Drug Interactions on the Risk of Congenital Anomalies**

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**Short title:** Placental transporters and transporter-mediated drug interactions

Table A: The codings for each type of major anomalies included in the study

|  |  |  |
| --- | --- | --- |
| **Types of major anomalies** | **ICD 9** | **ICD 10** |
| Nervous system | 740-742 | Q00-Q07 (not Q0782) |
| Eye, ear, face & neck | 743-744 (not 74365, 74411-74413, 7443, 74491) | Q10-Q16, Q178, Q183, Q188 (not Q101-Q103, Q105, Q135) |
| Heart | 745-746,7470-7474 (not 74550) | Q20-Q26 (not Q2111) |
| Respiratory | 748 (not 74819, 748304, 74832, 74862) | Q30-Q34 (not Q309, Q314, Q315, Q320, Q331) |
| Oro-facial clefts | 7490-7492 | Q35-Q37 |
| Digestive system, excluding diaphragmatic hernia and including hypertrophic pyloric stenosis | 750-751 (not 7500, 75012, 75024, 7506, 7510) | Q38-Q45 (not Q381, Q382, Q3850, Q401, Q4021, Q430, Q4320, Q4381, Q4382) |
| Urinary | 75261, 753 (not 753101, 75334), 756721 | Q60-Q64 (not Q610, Q633), Q794 |
| Genital | 750-7524 (not 752431, 752442), 75260, 7527-7529 | Q50-Q52, Q54-Q56 (not Q544, Q5520, Q5521) |
| Limb | 75430, 75444, 75450, 75451, 754731, 7548, 7550-7554, 755505-755507, 75551, 755522, 75553, 755552-75559, 755612-7559 | Q65-Q74 (not Q653-Q656, Q662-Q669, Q67, Q680, Q6821, Q683-Q685, Q7400) |

Table B: Risk of overall anomalies in cases exposed to drug-drug interactions mediated by placental transporter proteins

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Drug interaction patterns** | **All cases** | | **Liveborn cases only** | |
| Cases (N=5,131) | Referent population (N=31,055) | Live-born cases (N=4,805) | Referent population (N=31,055) |
| **BCRP** | | | | |
| BCRP substratesa  alone, n (%) | 150 (2.9) | 1101 (3.5) | 134 (2.8) | 1101 (3.5) |
| BCRP substratesa  + inhibitor, n (%) | 3 (0.06) | 31 (0.01) | 3 (0.06) | 31 (0.01) |
| Unadjusted OR (95% CI) | 0.71 (0.22-2.35) | | 0.8 (0.24-2.64) | |
| Adjusted ORb (95% CI) | 0.69 (0.21-2.28) | | 0.78 (0.23-2.58) | |
| **MRP1** | | | | |
| MRP1substratesa alone, n (%) | 306 (6.0) | 2468 (7.9) | 287 (6.0) | 2468 (7.9) |
| MRP1 substrates a  + inhibitor, n (%) | 1 (0.02) | 4 (0.01) | 1 (0.02) | 4 (0.01) |
| Unadjusted OR (95% CI) | 2.02 (0.23-18.1) | | 2.15 (0.24-19.3) | |
| Adjusted ORb (95% CI) | 1.96 (0.22-17.70) | | 2.04 (0.23-18.46) | |
| **MCT1** | | | | |
| MCT1 substrates a alone, n (%) | 24 (0.47) | 45 (0.14) | 20 (0.42) | 45 (0.14) |
| MCT1 substrates a + inhibitor, n (%) | 1 (0.02) | 3 (0.001) | 1 (0.02) | 3 (0.001) |
| Unadjusted OR (95% CI) | 0.63 (0.062-6.34) | | 0.75 (0.073-7.66) | |
| Adjusted ORb (95% CI) | 0.61 (0.06-6.26) | | 0.74 (0.072-7.66) | |
| **BCRP-OATP2B1** | | | | |
| BCRP-OATP2B1 substrates a alone, n (%) | 150 (2.9) | 1098 (3.5) | 134 (2.8) | 1098 (3.5) |
| BCRP-OATP2B1 substrates a + inhibitor, n (%) | 3 (0.06) | 34 (0.11) | 3 (0.06) | 34 (0.11) |
| Unadjusted OR (95% CI) | 0.65 (0.2-2.13) | | 0.72 (0.22-2.39) | |
| Adjusted ORb (95% CI) | 0.62 (0.19-2.05) | | 0.70 (0.21-2.33) | |

BCRP: breast cancer resistance protein; MRP: multidrug-associated protein; MCT: monocarboxylate transporter; OATP: organic anion transporting polypeptide; aincludes substrates and substrates/inhibitors; badjusted for maternal age and child gender

Table C: List of placental transporter proteins included in the study and the respective drug substrates/inducers/inhibitors

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Placental transporters** | **Encoding genes** | **Localization at the placental barrier** | **Efflux or influx** | **Expression level\*** | **Substrates** | **Substrates/Inhibitors** | **Inhibitors** | **Inducers** |
| Breast cancer resistance protein, BCRP | *ABCG2* | Apical | Efflux | 0.0954 | Cimetidine, Abacavir, Lamivudine, Prazosin, Rosuvastatin, Glibenclamide, Cervivastatin, Zidovudine, Methotrexate, Furosemide, Etoposide, Daunorubicin, Doxorubicin, Epirubicin, Grepafloxacin, Erlotinib, Lapatinib, Topotecan, Irinotecan, Flavonoids, Nitrofurantoin, Ciprofloxacin, Ofloxacin, Norfloxacin, Ulifoxacin, Erythromycin, Albendazole, Pitavastatin, Hydrochlorothiazide, Triamterene, Dantrolene, Riboflavin, Adefovir, Sulfasalazine [1–5] | Lopinavir, Delavirdine, Efavirenz, Atazanavir, Imatinib, Gefitinib [6] | Dipyridamole, Saquinavir, Ritonavir, Nelfinavir, Cyclosporine, Tamoxifen, Tacrolimus, Sirolimus, Nicardipine, Nitrendipine, Nimodipine, Reserpine, Omeprazole [4,7,8] |  |
| Organic cation transporter 3, OCT3 | *SLC22A3* | Basolateral | Influx | 0.146 | Epinephrine, Histamine, Norepinephrine, Amiloride, Amphetamines  [9–12] | Cimetidine, Impiramine, Despiramine, Clonidine, Procainamide, Flecainide, Amiodarone, Verapamil, Diltiazem, Citalopram, Amitriptyline, Cisplatine, Oxaliplatine, Abacavir, Emtricitabine, Saquinavir, Tenofovir, Lamivudine, Ritonavir, Indinavir, Nelfinavir, Ranitidine, Metformin, Cocaine, Fexofenadine  [6] | Quinidine, Rifampicin, Prazosin, Phenoxybenzamine, Progesterone, Amantadine, Ketamine, Memantine, Quinine, Atropine, Diphenhydramine, Etilefrine, Famotidine, Pentamidine, Phenformin [13] |  |
| Organic anion transporter 4, OAT4 | *SLC22A11* | Basolateral | Influx | 0.106 |  | Pravastatin, Tetracycline, Zidovudine, Valproic acid, Methotrexate, Ketoprofen  [6,10] | Probenecid, Captopril, Olmesartan, Telmisartan, Candesartan, Losartan, Pratosartan, Valsartan, Ethacrynate, Furosemide, Torasemide, Bumetanide, Acetazolamide, Trichlormethiazide, Chlorothiazide, Cefadroxil, Cefazolin, Cefoperazone, Cefotaxime, Ceftriaxone, Diflunisal, Phenylbutazone, Sulfinpyrazone  [4,10,14] |  |
| Multidrug-associated resistance protein 1, MRP1 | *ABCC1* | Basolateral | Efflux | 0.0224 | Cisplatin, Methotrexate, Etoposide, Vincristine, Vinblastine, Daunorubicin, Doxorubicin, Epirubicin, Folic Acid, Grepafloxacin, Glutathione, Leukotrien  [5,12,15] | Abacavir, Emtricitabine, Tenofovir, Lamivudine, Ritonavir, Indinavir, Lopinavir, Delavirdine, Efavirenz, Nevirapine, Atazanavir [6,15] | Cyclosporine, Probenecid, Sulfinpyrazone, Indometachin  [15,16] | Saquinavir [10] |
| Organic anion transporting polypeptide 2B1, OATP2B1 | *SLCO2B1* | Basolateral | Influx | 0.0557 | Fluvastatin, Rosuvastatin, Benzylpenicillin, Bosentan, Unoprostone  [17–19] | Saquinavir, Nelfinavir, Fexofenadine, Atorvastatin, Pravastatin, Glibenclamide, Repaglinide, Lopinavir, Estrone-3-sulfate  [6] | Ritonavir, Indinavir, Rifampicin, Rifamycin, Cyclosporine, Gemfibrozil, Cerivastatin, Paclitaxel, Rosiglitazone, Simvastatin  [6] |  |
| Equilibrative nucleoside transporter, ENT1 | *SLC29A1* | Apical | Influx | 0.0656 | Adenosine, Cladribine, Clofarabine, Gemcitabine, Ribavirin, Tiazofurin [5] |  | Dipyridamole, Dilazep [11] |  |
| Monocarboxylate transporter 1, MCT1 | *SLC16A1* | Basolateral | Influx | 0.091 | Dipyridamole, Dilazep, Atorvastatin, Pravastatin, Valproic acid, Salicylic acid [12] |  | Ketoprofen, Probenecid, Ibuprofen, Gabapentin [20,21] |  |
| Monocarboxylate transporter 4, MCT4 | *SLC16A3* | Apical | Influx | 4.99 | Valproic acid [12] |  | Atorvastatin, Fluvastatin, Cerivastatin, Simvastatin, Lovastatin [20–22] |  |
| Monocarboxylate transporter 8, MCT8 | *SLC16A2* | Apical | Influx | 0.0442 |  |  | Probenecid, Ketoprofen, Despiramine [20,23] |  |
| Monocarboxylate transporter 10, MCT10 | *SLC16A10* | Apical | Influx | 0.0203 |  |  | Probenecid, Ketoprofen, Despiramine [20,23] |  |

\*ratio of transporter protein mRNA to PPIA (peptidylprolyl isomerase A) mRNA

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