# Over-the-counter analgesics during pregnancy: a comprehensive review of global prevalence and offspring safety

<table>
<thead>
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<th>Journal:</th>
<th><em>Human Reproduction Update</em></th>
</tr>
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<td>HRU-20-0019.R2</td>
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<td>Manuscript Type:</td>
<td>Review</td>
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<tr>
<td>Date Submitted by the Author:</td>
<td>n/a</td>
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<tr>
<td>Complete List of Authors:</td>
<td>Zafeiri, Aikaterini; University of Aberdeen, Institute of Medical Sciences Mitchell, Rod; University of Edinburgh, MRC Centre for Reproductive Health Hay, David; The University of Edinburgh MRC Centre for Reproductive Health Fowler, Paul A; University of Aberdeen, Institute of Medical Sciences</td>
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<td>Keywords:</td>
<td>over-the-counter, non-prescription, analgesics, fetal exposure, acetaminophen, paracetamol, ibuprofen, aspirin, diclofenac, PREGNANCY</td>
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</tbody>
</table>
Figure 1. Prevalence of analgesics consumption during pregnancy from different parts of the world. Percentages summarised here as reported by the literature. More details on each study can be found in Table 1 and in text.

338x190mm (300 x 300 DPI)
Figure 2. Schematic diagram of the major drug transporters on human placental syncytiotrophoblast and their substrates according to medication type. Solute-linked carrier (SLC) (blue) and adenosine triphosphate binding cassette (ABC) transporters (red). Phase I metabolising enzymes (P1); phase II metabolising enzymes (P2). Arrow direction demonstrates influx/efflux. Note that not all substrates have been examined in the human placenta. Figure was prepared based on information cited in this review. * exact placental membrane localisation not known; † localised on both membranes.
Figure 3. OTC analgesic exposures during pregnancy and their associations with adverse offspring health outcomes from current literature. Indication of references according to study type: * Cohort Studies, § Case-control/Case Report Studies, ¥ Systematic reviews/Meta-analyses, † Experimental Studies
Table 1. Proportion of women using analgesics during pregnancy. Data from various studies across global regions.

<table>
<thead>
<tr>
<th>Country</th>
<th>Study Period</th>
<th>Gestational Period</th>
<th>Cohort size (n)</th>
<th>Data collection method</th>
<th>Analgesics use (%)</th>
<th>OTC Analgesics</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Denmark</td>
<td>2010-2012</td>
<td>1st and 2nd trimester</td>
<td>1,027</td>
<td>Questionnaires</td>
<td>39.9</td>
<td>Paracetamol</td>
<td>Lind et al., 2017</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4.4</td>
<td>Ibuprofen/Aspirin</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>39.2</td>
<td>(Paracetamol most common)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>39.0</td>
<td>Paracetamol NSAIDs</td>
<td></td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>4.5</td>
<td>Paracetamol Aspirin</td>
<td></td>
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<tr>
<td>Australia, Europe, America</td>
<td>2011-2012</td>
<td>All trimesters</td>
<td>9,459</td>
<td>Online questionnaires</td>
<td>47.7</td>
<td>Paracetamol NSAIDs</td>
<td>Lupattelli et al., 2014</td>
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<tr>
<td>USA</td>
<td>1998-2005</td>
<td>All trimesters</td>
<td>10,533</td>
<td>Interviews</td>
<td>65.5</td>
<td>Paracetamol Ibuprofen</td>
<td>Werler et al., 2005</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4.5</td>
<td>Aspirin</td>
<td></td>
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<tr>
<td>USA</td>
<td>2004-2009</td>
<td>1st trimester</td>
<td>5,381</td>
<td>Interviews</td>
<td>55.8</td>
<td>Paracetamol Ibuprofen</td>
<td>Thorpe et al., 2013</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>23.5</td>
<td>Aspirin</td>
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<tr>
<td>USA (Hispanic population)</td>
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<td>Did not ascertain</td>
<td>485</td>
<td>Questionnaires</td>
<td>13</td>
<td>Paracetamol Ibuprofen</td>
<td>Bercaw et al., 2010</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4</td>
<td>Aspirin</td>
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</tr>
<tr>
<td>Middle East</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3</td>
<td>Paracetamol Ibuprofen</td>
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<tr>
<td>United Arab Emirates</td>
<td>October to December 2016</td>
<td>&quot;varying&quot; trimesters</td>
<td>140</td>
<td>Questionnaires</td>
<td>55.1</td>
<td>Paracetamol Ibuprofen</td>
<td>Abdulkarem &amp; Mustafa, 2017</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10.3</td>
<td>Aspirin</td>
<td></td>
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<tr>
<td>Saudi Arabia</td>
<td>April and May 2017</td>
<td>All trimesters</td>
<td>100</td>
<td>Questionnaires</td>
<td>14</td>
<td>Paracetamol Ibuprofen</td>
<td>Al Bahhawi et al., 2018</td>
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<tr>
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<td>4</td>
<td>Aspirin</td>
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<tr>
<td>Iran</td>
<td>Not specified</td>
<td>Not specified</td>
<td>180</td>
<td>Questionnaires</td>
<td>&gt;35</td>
<td>General OTC medication</td>
<td>Baghianimoghadam et al., 2013</td>
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<tr>
<td>Country</td>
<td>Period</td>
<td>Study Design</td>
<td>No.</td>
<td>Type</td>
<td>NSAIDs</td>
<td>Authors, Year</td>
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<tr>
<td>Pakistan</td>
<td>April to October 2014</td>
<td>All trimesters</td>
<td>351</td>
<td>Interviews</td>
<td>Paracetamol</td>
<td>Bohio et al., 2016</td>
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<tr>
<td>Ethiopia</td>
<td>February to March 2012</td>
<td>All trimesters</td>
<td>339</td>
<td>Patient records and interviews</td>
<td>Paracetamol</td>
<td>Mohammed et al., 2013</td>
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<td>All trimesters</td>
<td>1,268</td>
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<td>Kebede et al., 2009</td>
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<tr>
<td>Nigeria</td>
<td>Not specified</td>
<td>All trimesters</td>
<td>518</td>
<td>Questionnaires</td>
<td>Not specified</td>
<td>Abasiubong et al., 2012</td>
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Table 2. Drug transporters localised on human placenta and their known substrates

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<tr>
<th>Transporter</th>
<th>Placenta membrane localisation</th>
<th>Direction of transport</th>
<th>OTC analgesics</th>
<th>Others</th>
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<tr>
<td><strong>ABCB1</strong></td>
<td>Apical</td>
<td>Efflux</td>
<td>Aspirin metabolites</td>
<td>Anticancer drugs, antibiotics, HIV protease inhibitors, morphine</td>
<td>(Kim, 2002)</td>
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<td><strong>ABCG2</strong></td>
<td>Apical</td>
<td>Efflux</td>
<td>Paracetamol metabolites</td>
<td>Chemotherapeutic agents, antiretroviral medications, antibiotics, glyburide (hypoglycemic agent)</td>
<td>(Mao and Unadkat, 2015)</td>
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<tr>
<td><strong>ABCC1</strong></td>
<td>Apical and basal</td>
<td>Efflux</td>
<td>Antibiotics, antimicrobial agents, Hepatitis B inhibitors, HIV inhibitors, anticancer medications</td>
<td>(Renes et al., 1999; Olson et al., 2002)</td>
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<tr>
<td><strong>ABCC2</strong></td>
<td>Apical</td>
<td>Efflux</td>
<td>Paracetamol metabolites</td>
<td>Antibiotics, antineoplastic compounds, antibacterial agents, AIDS inhibitors, HIV inhibitors</td>
<td>(Bakos et al., 2000; St-Pierre et al., 2000; Grube et al., 2005; Meyer zu Schwabedissen et al., 2005)</td>
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<td><strong>ABCC3</strong></td>
<td>Apical</td>
<td>Efflux</td>
<td>Paracetamol metabolites</td>
<td>Antihistaminic agents, antineoplastic compounds</td>
<td>(St-Pierre et al., 2000; Azzaroli et al., 2007; Ni and Mao, 2011)</td>
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<td><strong>ABCC4</strong></td>
<td>Apical</td>
<td>Efflux</td>
<td>Paracetamol metabolites</td>
<td>Antibacterial agents, antiviral agents, antihypertension agents, diuretic medications</td>
<td>(Ritter et al., 2005; Azzaroli et al., 2007; Russel, Koenderink and Masereeuw, 2008)</td>
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<td><strong>ABCC5</strong></td>
<td>Basal</td>
<td>Efflux</td>
<td>Antineoplastic agents, Hepatitis B inhibitors, statins</td>
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<td>(Meyer zu Schwabedissen et al., 2005)</td>
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<tr>
<td>Transporter</td>
<td>Localization</td>
<td>Direction</td>
<td>Substrates</td>
<td>References</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>OCT3/SLC22A3</td>
<td>Basal</td>
<td>bidirectional</td>
<td>Cationic drugs, nicotine, amphetamine</td>
<td>(Sata et al., 2005; Lee et al., 2018)</td>
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<tr>
<td>OCTN1/SLC22A4</td>
<td>Apical</td>
<td>bidirectional</td>
<td>Respiratory agents, anti-viral compounds, anticancer drugs</td>
<td>(Koepsell, 2004; Nakamura et al., 2010; Mukherjee et al., 2013; Yang et al., 2016)</td>
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<tr>
<td>OCTN2/SLC22A5</td>
<td>Apical</td>
<td>bidirectional</td>
<td>Respiratory agents, anti-viral compounds, anticancer drugs</td>
<td>(Ohashi et al., 1999; Koepsell, 2004; Nakamura et al., 2010; Mukherjee et al., 2013; Yang et al., 2016)</td>
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<tr>
<td>OATP2B1/SLCO2B1</td>
<td>Basal</td>
<td>Influx</td>
<td>Aloskiren, atorvastin, benzylpenicillin</td>
<td>(St-Pierre et al., 2000; Ugele et al., 2003; Roth, Obaidat and Hagenbuch, 2012)</td>
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<td>OATP4A1/SLCO4A1</td>
<td>Apical</td>
<td>Influx</td>
<td>Benzylpenicillin, thyroxine (T4), triiodothyronine (T3)</td>
<td>(Tamai et al., 2000; Fujiwara et al., 2001)</td>
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<td>OAT4/SLC22A11</td>
<td>Basal</td>
<td>Influx</td>
<td>NSAIDs</td>
<td>Antihypertensive compounds</td>
<td>(Cha et al., 2000; Ugele et al., 2003; Rizwan and Burckhardt, 2007; Nigam et al., 2015; Noguchi et al., 2015)</td>
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<td>OAT1/SLC22A6</td>
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<td>Aspirin metabolites</td>
<td>Antiviral agents, antibacterial agents, anticancer drugs, statins, antibiotics</td>
<td>(Rizwan and Burckhardt, 2007; Reese et al., 2016)</td>
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<tr>
<td>SERT/SLC6A4</td>
<td>Apical</td>
<td>Influx</td>
<td>Amphetamines, amphetamine derivatives, antidepressants, ADHD medication (atomoxetine)</td>
<td>(Madras et al., 2005; Velasquez et al., 2013)</td>
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<tr>
<td>NET/SLC6A5</td>
<td>Apical</td>
<td>Influx</td>
<td>Amphetamines, amphetamine derivatives, antidepressants, ADHD medication (atomoxetine)</td>
<td>(Madras et al., 2005; Velasquez et al., 2013)</td>
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<tr>
<td>Study details</td>
<td>Analgesic</td>
<td>Study time</td>
<td>Study type</td>
<td>Cohort</td>
<td>Data collection method</td>
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<td><strong>Analgesic</strong></td>
<td><strong>Study time</strong></td>
<td><strong>Study type</strong></td>
<td><strong>Cohort</strong></td>
<td><strong>Data collection method</strong></td>
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<td>Neurodevelopment</td>
<td>Paracetamol</td>
<td>1996-2002</td>
<td>Prospective cohort study</td>
<td>64,322 participants</td>
<td>Telephone interviews</td>
</tr>
<tr>
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<td>Paracetamol</td>
<td>1995-1997</td>
<td>Prospective follow-up cohort study</td>
<td>871 participants</td>
<td>Questionnaires, parent reports of children ADHD symptoms</td>
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<td></td>
<td>Paracetamol</td>
<td>1991-1992</td>
<td>Prospective cohort study</td>
<td>7,796 participants</td>
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<td>Paracetamol</td>
<td>Included studies up to January 2017</td>
<td>Systematic review, meta-analysis and meta-regression analysis</td>
<td>132,738 participants from 7 cohort studies</td>
<td>Searches in MEDLINE, Embase and Cochrane databases</td>
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<td></td>
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<td>Systematic review and meta-analysis</td>
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<td>Searches in PubMed, Embase, Web of Science and Cochrane databases</td>
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<td>1999-2008</td>
<td>Sibling-controlled cohort study</td>
<td>48,631 participants</td>
<td>Questionnaires</td>
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<td>Drug</td>
<td>Years</td>
<td>Type of Study</td>
<td>Participants</td>
<td>Methodology</td>
<td>Findings</td>
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<tr>
<td>Paracetamol</td>
<td>1996-2002</td>
<td>Prospective cohort study</td>
<td>64,322</td>
<td>Telephone interviews</td>
<td>Higher risk for ASD with hyperkinetic symptoms</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>1991-1992</td>
<td>Prospective cohort study</td>
<td>14,062</td>
<td>Questionnaires</td>
<td>Adverse association with pre-school children behaviour</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>2007-2010</td>
<td>Population-based prospective study</td>
<td>754</td>
<td>Maternal reports and paracetamol urinary concentration measurements</td>
<td>Significant association with language delay in girls at 30 months of age</td>
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<td>Paracetamol,</td>
<td>1996-2002</td>
<td>Prospective cohort study</td>
<td>185,617</td>
<td>Questionnaires and telephone interviews</td>
<td>Higher risk for spastic CP</td>
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<td>aspirin</td>
<td>1999-2008</td>
<td>(two cohorts)</td>
<td></td>
<td></td>
<td></td>
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<td>Paracetamol,</td>
<td>1974-1975</td>
<td>Prospective cohort study</td>
<td>421</td>
<td>Interviews and laboratory examinations of children</td>
<td>Decrease in IQ levels at 4 years of age after maternal consumption of aspirin during pregnancy</td>
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<tr>
<td>aspirin</td>
<td>1968-1980</td>
<td>Retrospective population-based case control study</td>
<td>385 infants with NTD and 2,676 control infants</td>
<td>Interviews</td>
<td>Increased incidence of NTDs when consumed to treat flu symptoms</td>
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<td>Aspirin</td>
<td>1997</td>
<td>Retrospective cohort study</td>
<td>656</td>
<td>Questionnaires</td>
<td>No association between low-dose aspirin consumption and adverse offspring neurodevelopmental</td>
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<td>Study Type</td>
<td>Participants</td>
<td>Methodology</td>
<td>Outcome</td>
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<td>-------------------------------------------------</td>
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<td>1959-1966</td>
<td>Prospective cohort</td>
<td>19,226</td>
<td>Interviews and follow-up examinations of children</td>
<td>No association with decreased IQ levels at 4 years of age</td>
</tr>
<tr>
<td>Aspirin</td>
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<td>Longitudinal cohort</td>
<td>6,437</td>
<td>Questionnaires</td>
<td>Increased risk of offspring psychotic experiences during adolescence</td>
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<td>NSAIDs, aspirin</td>
<td>2002-2004</td>
<td>Prospective cohort</td>
<td>877</td>
<td>Interviews</td>
<td>Increased risk of preterm infants developing CP</td>
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<td>Study details</td>
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<td>Study time</td>
<td>Study type</td>
<td>Cohort</td>
<td>Data collection method</td>
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<td>Outcome Category</td>
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<td>1999-2008</td>
<td>Prospective cohort study</td>
<td>53,169 participants</td>
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<td></td>
<td>Paracetamol</td>
<td>1999-2002</td>
<td>Prospective cohort study</td>
<td>1,490 participants</td>
<td>Interviews and questionnaires</td>
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<td>1997-2009</td>
<td>Prospective cohort study</td>
<td>1,505 participants</td>
<td>Interviews</td>
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<td>Systematic review and meta-analysis</td>
<td>6 studies</td>
<td>Searches in Medline, EMBASE, Cochrane and Cochrane Database of Systematic Reviews</td>
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<td>Paracetamol</td>
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<td>Randomised controlled trial</td>
<td>345 participants</td>
<td>Questionnaires</td>
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<td>Paracetamol</td>
<td>1998-2006</td>
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<td>301 participants</td>
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<td>Association of use during middle and late pregnancy with offspring wheeze at 5 years of age</td>
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<td>Study details</td>
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<td>Study time</td>
<td>Study type</td>
<td>Cohort</td>
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<td><strong>Testes</strong></td>
<td>Ibuprofen</td>
<td>n/a</td>
<td><em>Ex-vivo</em> and xenograft systems</td>
<td>First and second trimester human fetal testes</td>
<td>n/a</td>
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<td></td>
<td>Paracetamol, aspirin</td>
<td>n/a</td>
<td><em>Ex-vivo</em> system</td>
<td>First trimester human fetal testes</td>
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<td></td>
<td>Exact compound not specified</td>
<td>1987-1990</td>
<td>Nested case-control study</td>
<td>6,699 male neonates</td>
<td>Questionnaires and examinations for cryptorchidism</td>
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<td>Paracetamol, aspirin</td>
<td>Not specified</td>
<td>Prospective cohort study</td>
<td>1,954 participants</td>
<td>Questionnaires and interviews</td>
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<tr>
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<td>2001-2009</td>
<td>Prospective cohort study</td>
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<td>Questionnaires</td>
</tr>
<tr>
<td></td>
<td>Paracetamol, NSAIDs</td>
<td>2010-2012</td>
<td>Prospective birth cohort study</td>
<td>1,027 participants</td>
<td>Interviews and examinations</td>
</tr>
<tr>
<td>Drug</td>
<td>Year</td>
<td>Design</td>
<td>Participants</td>
<td>Data Collection</td>
<td>Summary</td>
</tr>
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</tr>
<tr>
<td>Aspirin</td>
<td>1982-1989</td>
<td>Prospective survey</td>
<td>56,037 participants</td>
<td>Forms completed by the doctor</td>
<td>Higher risk for hypospadias when consumed during the 1st trimester</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>1977-2007</td>
<td>Case-control study</td>
<td>1,537 infants with hypospadias, 4,314 controls</td>
<td>Interviews</td>
<td>Higher risk for hypospadias</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>1997-2005</td>
<td>Case-control study</td>
<td>14,915 birth defect cases, 5,546 controls</td>
<td>Interviews</td>
<td>No significant association with hypospadias</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Not specified</td>
<td>Retrospective cohort study</td>
<td>50,282 participants</td>
<td>Interviews and reviews of clinical records</td>
<td>No significant association with hypospadias</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>2002-2006</td>
<td>Prospective cohort study</td>
<td>3,184 participants</td>
<td>Physical examinations, questionnaires, interviews and biological samples</td>
<td>Higher risk for cryptorchidism when consumed in the 2nd trimester No association with hypospadias</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>n/a</td>
<td>Xenograft system</td>
<td>14 human fetal testes</td>
<td>n/a</td>
<td>Reduced testicular testosterone production</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>1996-2002</td>
<td>Retrospective cohort study</td>
<td>47,400 participants</td>
<td>Interviews and questionnaires</td>
<td>Higher risk for cryptorchidism</td>
</tr>
<tr>
<td>Paracetamol, Aspirin, ibuprofen</td>
<td>2003-2006</td>
<td>Retrospective cohort study</td>
<td>903 participants</td>
<td>Questionnaires</td>
<td>No significant association with cryptorchidism (Philippat et al., 2011)</td>
</tr>
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</tr>
<tr>
<td>Ovaries</td>
<td>Ibuprofen</td>
<td>n/a</td>
<td>Ex-vivo system</td>
<td>185 human fetal ovaries</td>
<td>Effect on ovarian cell proliferation and germ cell number during the 1st trimester (Leverrier-Penna et al., 2018)</td>
</tr>
<tr>
<td>Paracetamol, ibuprofen</td>
<td>n/a</td>
<td>Ex-vivo system</td>
<td>3 human fetal ovaries</td>
<td>n/a</td>
<td>Significant reduction in ovarian germ cell number (Hurtado-Gonzalez et al., 2018)</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>2012-2017</td>
<td>Longitudinal cohort study</td>
<td>15,822 participants</td>
<td>Interviews and questionnaires</td>
<td>Earlier onset of pubertal events in female offspring (Ernst et al., 2019)</td>
</tr>
</tbody>
</table>
Table 6. Studies on cardiovascular offspring outcomes following *in utero* exposure to OTC analgesics

<table>
<thead>
<tr>
<th>Outcome Category</th>
<th>Analgesic</th>
<th>Study time</th>
<th>Study type</th>
<th>Cohort</th>
<th>Data collection method</th>
<th>Main study results</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>Paracetamol</td>
<td>Studies up to June 2018</td>
<td>Case series analysis</td>
<td>25 cases of fetal ductus arteriosus constriction or closure from 12 papers</td>
<td>Searches in PubMed, Web of Science and Google Scholar</td>
<td>Likely causal relationship between fetal ductus arteriosus constriction or closure and maternal intake (Allegaert <em>et al.</em>, 2019)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diclofenac</td>
<td>2015</td>
<td>Case report</td>
<td>1 case</td>
<td>Case description</td>
<td>Association with fetal ductus arteriosus constriction or closure</td>
<td>(Aker <em>et al.</em>, 2015)</td>
</tr>
<tr>
<td></td>
<td>NSAIDs</td>
<td>1995-1998</td>
<td>Prospective cohort study</td>
<td>2,557 participants</td>
<td>Interviews</td>
<td>Association with cardiac defects following use in early pregnancy</td>
<td>(Ericson and Källén, 2001)</td>
</tr>
<tr>
<td></td>
<td>Paracetamol</td>
<td>1997-2011</td>
<td>Case-control study</td>
<td>29,078 birth defect cases and 10,962 controls</td>
<td>Interviews, pregnancy calendars, questionnaires</td>
<td>Higher risk of cardiac defects following consumption of paracetamol compared to other NSAIDs</td>
<td>(Interrante <em>et al.</em>, 2017)</td>
</tr>
</tbody>
</table>
### Table 7. Studies on renal offspring outcomes following in utero exposure to OTC analgesics

<table>
<thead>
<tr>
<th>Study details</th>
<th>Analgesic</th>
<th>Study time</th>
<th>Study type</th>
<th>Cohort</th>
<th>Data collection method</th>
<th>Main study results</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Renal</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Diclofenac</td>
<td></td>
<td>Not specified</td>
<td>Case report</td>
<td>2 cases</td>
<td>Case description</td>
<td>Oligohydramnios on both cases during the 2nd trimester</td>
<td>(Scherneck et al., 2015)</td>
</tr>
<tr>
<td>Diclofenac</td>
<td></td>
<td>Not specified</td>
<td>Case report</td>
<td>3 cases</td>
<td>Case description</td>
<td>Irreversible association with neonatal renal failure and oliguria</td>
<td>(Phadke et al., 2012)</td>
</tr>
<tr>
<td>Aspirin</td>
<td></td>
<td>1991-1992</td>
<td>Clinical trial</td>
<td>32 aspirin-treated 27 placebo-treated participants</td>
<td>n/a</td>
<td>No significant association of low-dose aspirin with amniotic fluid volume or fetal urine output</td>
<td>(Maher et al., 1993)</td>
</tr>
<tr>
<td>Paracetamol</td>
<td></td>
<td>2008-2019</td>
<td>Prospective cohort study</td>
<td>604 pregnancies exposed during the 3rd trimester 1,192 pregnancies exposed only during 1st and 2nd trimester</td>
<td>Questionnaires</td>
<td>No significant association with fetal renal toxicity during the 3rd trimester</td>
<td>(Dathe et al., 2019)</td>
</tr>
</tbody>
</table>
Table 9. Studies on pregnancy outcomes following *in utero* exposure to OTC analgesics

<table>
<thead>
<tr>
<th>Study details</th>
<th>Analgesic</th>
<th>Study time</th>
<th>Study type</th>
<th>Cohort</th>
<th>Data collection method</th>
<th>Main study results</th>
<th>Study</th>
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<tbody>
<tr>
<td>Outcome Category</td>
<td>Pregnancy outcome</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>NSAIDs</td>
<td>1977-1998</td>
<td>Cohort and case-control study</td>
<td>Cohort: 1,462 women with NSAID prescription 17,259 women without prescription Case-control: 4,268 miscarriage cases 29,750 live birth controls</td>
<td>Prescription records, diagnosis records</td>
<td>Higher risk of miscarriage, no association with adverse birth outcome</td>
<td>(Nielsen et al., 2001)</td>
</tr>
<tr>
<td></td>
<td>NSAIDs</td>
<td>1996-1998</td>
<td>Prospective cohort study</td>
<td>1,055 participants</td>
<td>Interviews, medical records checks</td>
<td>Higher risk of miscarriage</td>
<td>(Li et al., 2003)</td>
</tr>
<tr>
<td></td>
<td>Ibuprofen</td>
<td>2000-2006</td>
<td>Retrospective cohort study</td>
<td>1,117 participants</td>
<td>Questionnaires</td>
<td>No significant association with spontaneous abortion or major birth defects</td>
<td>(Dathe et al., 2018)</td>
</tr>
<tr>
<td></td>
<td>NSAIDs</td>
<td>2003-2009</td>
<td>Retrospective cohort study</td>
<td>65,457 participants</td>
<td>Medical records and databases</td>
<td>No significant association with spontaneous abortion</td>
<td>(Daniel et al., 2014)</td>
</tr>
<tr>
<td></td>
<td>NSAIDs</td>
<td>2004-2010</td>
<td>Prospective cohort study</td>
<td>2,780 participants</td>
<td>Medical records and interviews</td>
<td>No significant association with spontaneous abortion</td>
<td>(Edwards et al., 2012)</td>
</tr>
<tr>
<td>Drug</td>
<td>Included studies up to 2001</td>
<td>Method</td>
<td>Number of Studies</td>
<td>Search Sources</td>
<td>Findings</td>
<td>Reference</td>
<td></td>
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</tr>
<tr>
<td>Aspirin</td>
<td>182 studies</td>
<td>Meta-analysis of randomised controlled studies</td>
<td>182 studies</td>
<td>Searches in Medline, Embase, Toxline, EBM Cochrane Database of Systematic Reviews and Reproductive Toxicology</td>
<td>No significant association with miscarriage</td>
<td>(Kozer et al., 2003)</td>
<td></td>
</tr>
<tr>
<td>NSAIDs</td>
<td>4,705 cases of spontaneous abortion</td>
<td>Nested case-control study</td>
<td>4,705 cases of spontaneous abortion</td>
<td>Medical records</td>
<td>Higher risk for spontaneous abortion</td>
<td>(Nakhai-Pour et al., 2011)</td>
<td></td>
</tr>
<tr>
<td>Study details</td>
<td>Analgesic</td>
<td>Study time</td>
<td>Study type</td>
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<td>Data collection method</td>
<td>Main study results</td>
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<tr>
<td><strong>Outcome Category</strong></td>
<td><strong>Analgesic</strong></td>
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<td><strong>Study type</strong></td>
<td><strong>Cohort</strong></td>
<td><strong>Data collection method</strong></td>
<td><strong>Main study results</strong></td>
<td><strong>Study</strong></td>
</tr>
<tr>
<td><strong>Other perinatal outcomes</strong></td>
<td>Paracetamol</td>
<td>1976-1998</td>
<td>Case-control study</td>
<td>73 cases with amnion rupture sequence</td>
<td>Interviews, Offspring malformations were identified at birth</td>
<td>Higher risk for amnion rupture sequence when used during the 1st pregnancy trimester</td>
<td>(Werler et al., 2003)</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>2009-2013</td>
<td>Prospective cohort study</td>
<td>2,291 participants</td>
<td>Interviews, Fetal growth assessed via ultrasound measurements</td>
<td>No association with growth of the fetus during pregnancy</td>
<td>(Smarr et al., 2019)</td>
<td></td>
</tr>
<tr>
<td>Paracetamol, aspirin</td>
<td>1995-1999</td>
<td>Case-control study</td>
<td>206 gastroschisis cases, 126 small intestinal atresia cases, 798 controls</td>
<td>Interviews, Offspring malformations were identified at birth</td>
<td>Higher risk for gastroschisis when consumed in early pregnancy</td>
<td>(Werler et al., 2002)</td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>Included studies up to 2000</td>
<td>Systematic review and meta-analysis</td>
<td>22 studies</td>
<td>Searches in Medline, Embase, Toxline and EBM Reviews-Cochrane Database of Systematic Reviews,</td>
<td>Higher risk for gastroschisis when consumed during the 1st trimester</td>
<td>(Kozer et al., 2002)</td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>Time Period</td>
<td>Study Design</td>
<td>Number</td>
<td>Outcomes</td>
<td>Findings</td>
<td>Reference</td>
<td></td>
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<tr>
<td>Aspirin, ibuprofen</td>
<td>1989-1990</td>
<td>Case-control</td>
<td>110 birth defect cases 220 controls</td>
<td>Questionnaires, Offspring malformations identified at birth – information on clinical records</td>
<td>Higher risk for gastroschisis when consumed during the 1st trimester</td>
<td>(Torfs et al., 1996)</td>
<td></td>
</tr>
<tr>
<td>Diclofenac</td>
<td>1988-2008</td>
<td>Prospective cohort study</td>
<td>145 pregnant women exposed to diclofenac 501 controls</td>
<td>Questionnaires and interviews</td>
<td>No significant association with major birth defects following consumption during the 1st trimester</td>
<td>(Cassina et al., 2010)</td>
<td></td>
</tr>
<tr>
<td>Diclofenac</td>
<td>2000-2015</td>
<td>Prospective cohort study</td>
<td>260 women exposed to diclofenac 778 controls</td>
<td>Questionnaires and interviews</td>
<td>No significant association with major birth defects or spontaneous abortion following consumption during the 1st trimester</td>
<td>(Padberg et al., 2018)</td>
<td></td>
</tr>
<tr>
<td>NSAIDs</td>
<td>1999-2006</td>
<td>Prospective cohort study</td>
<td>69,929</td>
<td>Questionnaires, offspring birth defects identified in the first week after birth</td>
<td>No significant association with major birth defects following consumption during the 1st trimester</td>
<td>(van Gelder et al., 2011)</td>
<td></td>
</tr>
<tr>
<td>NSAIDs</td>
<td>1997-2001</td>
<td>Case-control study</td>
<td>29,078 birth defect cases and 10,962 controls</td>
<td>Interviews, pregnancy calendars, questionnaires</td>
<td>Higher risk for major birth defects compared to paracetamol</td>
<td>(Interrante et al., 2017)</td>
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</tr>
<tr>
<td>Paracetamol (overdose during pregnancy)</td>
<td>1976-1985</td>
<td>Case study</td>
<td>60 cases</td>
<td>Telephone consultation and detection of paracetamol plasma concentrations</td>
<td>No association with birth defects, significant association of time to treatment with spontaneous abortion and fetal death</td>
<td>(Riggs et al., 1989)</td>
<td></td>
</tr>
<tr>
<td>Paracetamol (overdose during pregnancy)</td>
<td>1984-1992</td>
<td>Case study</td>
<td>300 cases</td>
<td>Questionnaires</td>
<td>No association with birth defects or pregnancy termination</td>
<td>(McElhatton et al., 1997)</td>
<td></td>
</tr>
</tbody>
</table>
Title: Over-the-counter analgesics during pregnancy: a comprehensive review of global prevalence and offspring safety

Running Title: Over-the-counter analgesia during pregnancy

Authors: Aikaterini Zafeiri¹, Rod T Mitchell², David C Hay³, Paul A Fowler¹

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Reproductive defects

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Abstract

Background: Analgesia during pregnancy is often necessary. Due to their widespread availability, many mothers opt to use over-the-counter (OTC) analgesics. Those analgesic compounds and their metabolites can readily cross the placenta and reach the developing fetus. Evidence for safety or associations with adverse health outcomes is conflicting, limiting definitive decision-making for healthcare professionals.

Objective and rationale: This review provides a detailed and objective overview of research in this field. We consider the global prevalence of OTC analgesia during pregnancy, explain current mechanistic understanding of how analgesic compounds cross the placenta and reach the fetus, and review current research on exposure associations with offspring health outcomes.

Search Methods: A comprehensive English language literature search was conducted using PubMed and Scopus databases. Different combinations of key search terms were used including “over-the-counter/non-prescription analgesics”, “pregnancy”, “self-medication”, “paracetamol”, “acetaminophen”, “diclofenac”, “aspirin”, “ibuprofen”, “in utero exposure”, “placenta drug transport”, “placental transporters”, “placenta drug metabolism” and “offspring outcomes”.

Outcomes: This article examines the evidence of fetal exposure to OTC analgesia, starting from different routes of exposure to evidence, or the lack thereof, linking maternal consumption to offspring ill health. There is a very high prevalence of maternal consumption of OTC analgesics globally, which is increasing sharply. The choice of analgesia selected by pregnant women differs across populations. Location was also observed to have an effect on prevalence of use, with more developed countries reporting the highest consumption rates. Some of the literature focuses on
the association of \textit{in utero} exposure at different pregnancy trimesters and the
development of neurodevelopmental, cardiovascular, respiratory, reproductive
defects. This is in contrast to other studies which report no associations.

\textbf{Wider implications:} The high prevalence and the challenges of reporting exact
consumption rates make OTC analgesia during pregnancy a pressing reproductive
health issue globally. Even though some healthcare policy-making authorities have
declared consumption of some OTC analgesics for most stages of pregnancy safe,
such decisions are often based on partial review of literature. Our comprehensive
review of current evidence highlights that important knowledge gaps still exist. Those
areas require further research in order to provide pregnant mothers with clear
guidance with regard to OTC analgesic use during pregnancy.

\textbf{Keywords:} over-the-counter; non-prescription; analgesics; fetal exposure;
acetaminophen; paracetamol; ibuprofen; aspirin; diclofenac; pregnancy
**Introduction**

There is almost a complete lack of safety and efficacy profiling of medications during pregnancy. This includes failure to consider differences in fetal function and sensitivity to exogenous exposures depending upon gestational age or fetal sex. Since the exact mechanisms of action for many medications are not fully understood, drugs are best generally avoided during pregnancy when possible (Adam *et al.*, 2011). There are, however, some conditions that demand the use of prescription or over-the-counter (OTC) medications (Källén and Reis, 2016; Mitchell *et al.*, 2011).

The majority of women use at least one type of OTC medications during the course of their pregnancy, with analgesics being one of the most prevalent. OTC analgesics are generally considered safe at the recommended doses; however, dosage and frequency completely depend on the mother, and can vary with different levels of knowledge, often resulting in uncertainty and concern (Damase-Michel *et al.*, 2009; Pijpers *et al.*, 2017). The task of consulting and awareness-raising therefore falls on healthcare professionals. Such advice can sometimes, as in the case of developing countries, be based on inadequate knowledge (Alrabiah *et al.*, 2017; Pallivalapilla *et al.*, 2018).

Adverse side effects of OTC analgesics overconsumption in the adult are well known. Indeed, the association of paracetamol (also known as acetaminophen) overdose with liver failure and consequences of chronic use (Roberts *et al.*, 2016), have been exploited in the past, making paracetamol the most commonly used compound in self-poisoning in the US and UK (Kozer and Koren, 2001). Other OTC analgesics such as aspirin, non-steroidal anti-inflammatory drugs (NSAID), and their combinations with other drugs, can also have adverse effects on the cardiovascular
system and gastrointestinal tract of the adult. In sharp contrast there is a lack of adequate information regarding the safety of these medications during pregnancy, for both the mother and the fetus, which raises serious public health concerns (Adam et al., 2011). In this review, we discuss the prevalence of OTC analgesic consumption during pregnancy on a global scale. We describe trans-placental transport, as well as providing an overview of the current literature on the associations of in utero exposure and offspring postnatal ill health.

**Global prevalence of OTC analgesics amongst pregnant women**

The reality is that physicians recommend paracetamol to pregnant women to deal with common pregnancy symptoms, as it is considered to be the mildest and safest analgesic with the lowest risks of teratogenicity (Black and Hill, 2003). Paracetamol was classified as a “Pregnancy Category B” drug by the FDA in 2005 (www.fda.gov/Drugs). Members of this category were defined as a substance for which “animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women”. It has been known for many years that paracetamol can readily cross the placenta, as high concentrations and have been detected in fetal plasma samples, sometimes at levels matching those seen in the maternal liver (Byer et al., 1982; Nitsche et al., 2017). More widely, most NSAIDs can cross the placenta. Therefore, not only paracetamol, but other analgesics and their metabolites, can potentially have a direct effect on the developing fetus.

Indications of analgesics use without prescription during pregnancy are hard to quantify, as they are often subjective decisions of the mother. Most studies
assessing frequency of use during pregnancy and associations with adverse health outcomes in the offspring, very rarely take into account the reason of consumption in each case. They can vary from headaches, fever, injuries, infections, pregnancy-related pain, to chronic migraines or other secondary underlying conditions such as rheumatoid arthritis (Lalkhen and Grady, 2008; Negro et al., 2017; Ray-Griffith et al., 2018; Rivera Díaz and Lopera Rivera, 2012). Type and timing of the symptoms also determine short- or long-term use of analgesic compounds. Maternal pain relief from such conditions contributes towards physical and psychological well-being, which are important factors for an uneventful pregnancy. Individual compounds are used for the treatment of different conditions. Paracetamol is mainly used for its analgesic and antipyretic properties amongst pregnant women. NSAIDs, such as ibuprofen or diclofenac, are used to treat mild to moderate pain and fever. Aspirin can sometimes have a more specific purpose as it is often prescribed to treat conditions such as pre-eclampsia, recurrent miscarriages, fetal growth restriction (Atallah et al., 2017; Belhomme et al., 2017; Roberge et al., 2016). Over the counter, aspirin is also used as a painkiller and anti-inflammatory agent during pregnancy.

Quantifying the prevalence of OTC (non-prescription) analgesics consumption in pregnancy is not an easy task. A role in this has the fact that most studies on the topic fail to define whether consumption of such compounds that are available OTC occurs through maternal initiative, doctor prescription, or both. Studies from different countries around the world have employed approaches such as questionnaires, interviews and patient information systems in an attempt to measure consumption. Percentages of OTC analgesics use during pregnancy from different countries are summarised in Figure 1. A recent systematic review and meta-analysis, including 13
studies from African and Asian countries, reported an estimated overall prevalence of self-medication during pregnancy at 32% (Mohseni et al., 2018). In contrast, a multinational study on 9,459 women in Western Europe (Italy, Austria, Switzerland, France, United Kingdom, The Netherlands), Northern Europe (Norway, Sweden, Finland, Iceland), Australia, South America and North America (USA, Canada), showed that 50.6% used one or more types of OTC analgesics during pregnancy, with paracetamol being used most commonly (Lupattelli et al., 2014). A previous USA study revealed a similarly high percentage of 65.5% out of 10,533 pregnant women using paracetamol, some in combination with NSAIDs (Werler et al., 2005).

Another study in the USA investigated first trimester consumption by 5,381 mothers of healthy infants, and reported similar percentages (Thorpe et al., 2013). In Texas, a study, including only 485 Hispanic women, reported a general OTC medication use of 23%, with paracetamol, ibuprofen and aspirin used in 13%, 4% and 3% of the cases respectively (Bercaw et al., 2010). Most European countries have shown year on year increases in analgesics sales over the past 30 years (Kristensen et al., 2016). This is reflected in the high consumption rates of pregnant women in these populations. In Europe, a Danish study reported that almost 40% out of 1,027 women reported using paracetamol during pregnancy, while only 4.4% used ibuprofen or aspirin (Lind et al., 2017). A smaller study in France, analysing aspirin, paracetamol and ibuprofen use, showed that 81% out of 895 pregnant women used these compounds (Philippat et al., 2011). In the Netherlands, 29.9% of 3,184 women, used mild analgesics at some point during their pregnancy (Snijder et al., 2012). In neighbouring Germany, a more recent study of 518 women with singleton pregnancies, reported a 47.3% frequency of analgesics use, with paracetamol being again the most prevalent (Bremer et al., 2017). In the UK, a study including 14,199
pregnancies reported 39.6%, 39.2% and 30.9% use of analgesics during the 1st, 2nd and 3rd trimester respectively (Headley et al., 2004). Paracetamol was used most commonly, 10-15 times more than the next most frequently used compound. A study in southern Italy found that the most commonly used OTC medication was again paracetamol, consumed by 69.7% of 503 pregnant women. Interestingly 86.7% of these women reported that they were willing to self-medicate in case of a non-serious health problem (Navaro et al., 2018). In contrast, a considerably lower percentage of women consuming paracetamol during pregnancy (6.4%) was reported in a study from Serbia (Odalovic et al., 2012). This could be a result of differences in socio-demographic characteristics of the population in this country compared to the majority of the rest European countries (Mihailovic et al., 2018).

A small study in United Arab Emirates reported 55.1% and 10.3% out of 140 pregnant women using paracetamol and ibuprofen respectively (Abduelkarem and Mustafa, 2017). Among 100 pregnant women in Saudi Arabia, the most prevalent OTC analgesic was aspirin (14%), while paracetamol and ibuprofen were used less frequently (Al Bahhawi et al., 2018). In the developing country of Pakistan, a study in Hyderabad included 351 women and reported 43.6% of paracetamol, 3.8% ibuprofen and 1.5% aspirin use during their pregnancies (Bohio et al., 2016). A surprisingly high percentage of 77.4% of these women had no knowledge about the medicines they were choosing to use, including indications for use, doses and potential adverse side-effects. General OTC medication use among 180 pregnant women in Iran was higher than 35%; however, this study did not mention specific compounds (Baghianimoghadam et al., 2013). An Ethiopian study including 339 women, showed an OTC analgesics prevalence of 40.1% during pregnancy (Mohammed et al.,
In a larger study from the same country, general self-medication during pregnancy was reported for 12.4% out of 1,268 women, from who 19.2% and 1.9% used paracetamol and aspirin respectively (Kebede et al., 2009). In Nigeria, OTC analgesics were found to be used by 30.3% out of 518 pregnant women (Abasiubong et al., 2012).

Overall, as summarised in Table 1, there is a high global prevalence of OTC analgesic consumption during pregnancy. Because of the abundance and ease of access to these compounds, reported percentages might underestimate actual consumption levels, as most of these studies based their findings on questionnaires and/or interviews. In addition, under/overrepresentation of women of a certain educational level should not be overlooked when comparing populations from different countries. Nevertheless, at present cohort studies are the best tool to evaluate the frequency and dosage of analgesic use during pregnancy.

It is important to note that overall OTC analgesic consumption in the general population is high (Porteous et al., 2005; Samuelsen et al., 2015; Sarganas et al., 2015; Turunen et al., 2005). Some studies even report that women self-medicate more frequently than men, and this includes women of reproductive age (Dal Pizzol et al., 2019; Dale et al., 2015). OTC analgesics consumption has also been reported in pre-pregnancy cohorts of men and women trying to conceive (Palmsten et al., 2018). Therefore, a point to consider is that prospective pregnancies (pre-conception) could potentially be affected by early analgesic consumption, even before the individuals are aware of their pregnancy. However, we could not find any pre-pregnancy cohort studies assessing OTC analgesics consumption to date.
The feto-maternal interface and analgesics transport

Maternal and fetal blood circulations are separated throughout pregnancy (Boyd and Hamilton, 1970). However, essential communication between these two plasma units facilitates pregnancy maintenance, nutritional exchange and removal of fetal waste products, all utilising the placenta as a physical link. The placenta consists of endothelial cells of the fetal capillaries (basal membrane, fetal side) and syncytiotrophoblast cells (apical membrane, maternal side) (Elad et al., 2014). There are several mechanisms that facilitate feto-maternal communication depending on the nature of the molecule that is being transported. Specific transport can be by hydrophilic or lipophilic diffusion, and in some cases protein-mediated transport. Smaller molecules that have a maternal-fetal concentration gradient tend to simply diffuse across the placenta. The diffusion rate depends on the permeability and thickness of the placenta, the surface area available and the concentration difference. These parameters have been defined by a diffusion equation known as “Fick’s law” that is used to calculate the net rate of diffusion for any solute (Sibley et al., 2004). In addition, studies in rabbits have shown that despite the anatomical properties of the placenta, the fetal endothelium has a key role in determining drug transfer. This was also later described in humans by Elad and colleagues, which is biologically plausible, bearing in mind that these two species share the same hemochorial type of placenta (Elad et al., 2014).

Physiology and absorption, distribution, metabolism and excretion of drugs and their metabolites are altered during pregnancy and contribute to a change in maternal drug pharmacokinetics (Costantine, 2014; Feghali et al., 2015; Kazma et al., 2020; Pinheiro and Stika, 2020; Sen et al., 1998). Major changes in many organ systems
result in an altered maternal pharmacokinetic and pharmacogenomic profile during pregnancy; however, there are still many knowledge gaps on the topic (Betcher and George, 2020; Pariente et al., 2016). Gastrointestinal tract changes including common pregnancy symptoms such as constipation and gastric emptying, can impact drug absorption (Levy et al., 1994; Quinlan and Hill, 2010). Cardiac output, stroke volume, plasma volume, vascularity and blood flow to the uterus are also increased during pregnancy, which affect drug distribution (Capeless and Clapp, 1991; Pacheco et al., 2013; Pirani et al., 1973; Qasqas et al., 2004). In addition, the activity of several key phase I and II metabolising enzymes change during pregnancy, resulting in an altered drug metabolism (Betcher and George, 2020). Drug elimination is also increased during pregnancy through the increase in glomerular filtration rate (GFR) and overall renal elimination rate (Davison and Dunlop, 1984; Dunlop, 1981; Frederice et al., 2013). Finally, changes in placental transporter protein expression, further alter drug transport during pregnancy (Mathias et al., 2005; Sun et al., 2006). There are several approaches in the literature with pharmacokinetic models predicting and quantifying these changes during pregnancy (Van Hasselt et al., 2012; Jeong and Stika, 2020; Ke et al., 2014). A very relevant example is a study by Mian and colleagues, where paracetamol pharmacokinetics during pregnancy was successfully predicted using models in pregnant and non-pregnant women (Mian, Allegaert, et al., 2020).

As described, many drugs freely cross the placenta and reach the developing fetus. A number of researchers have been focusing on studying this ethically and practically constrained topic. In vitro models and animal studies are used in most cases, although extrapolation of results to humans can be problematic. Several in
models have been developed to study placental drug transfer and metabolism. *In vitro* models include placental cotyledon perfusion and cell cultures using placental explants, syncytiotrophoblasts, microvillus membrane vesicles and human placental choriocarcinoma cells (Syme *et al.*, 2004). *In vivo* studies in pregnant women have ethical and methodological restrictions limiting them to blood sampling from the mother (any peripheral vein) and the fetus (umbilical cord in the peri/post delivery period) for drug concentration ratio measurements. Animal *in vivo* models have been extensively used including experiments in mice, rats, sheep, rabbits, guinea pigs, and -for a closer to human approach- baboons and monkeys (e.g. macaques). Some studies have assessed coelomic and amniotic fluids, hair and meconium samples from the fetus to analyse intrauterine exposure to drugs and drug metabolites (Jauniaux and Gulbis, 2000; Ostrea *et al.*, 1989). The human placental perfusion model is another non-invasive way used to predict placental drug transfer *in vivo* (Hutson *et al.*, 2011). This method was used recently *ex vivo* on human term placenta to show the passive diffusion of paracetamol and the faster transport of two paracetamol metabolites through transporters (Conings *et al.*, 2019). A pharmacokinetic prediction model was developed recently to predict placental transfer, fetal metabolism and clearance of paracetamol (Mian, van den Anker, *et al.*, 2020).

Drugs in maternal plasma often exist in either an ionized form or bound to plasma proteins (serum albumin, lipoproteins, globulins, glycoproteins, etc) as well as being subject to transformation through oxidation, sulphation and/or glucuronidation. Only active drugs can diffuse through the placenta, meaning they must be unbound and unionized, unless they are transported in a conjugated form. While some drugs travel...
across the placenta through various active transport proteins, the majority, in their intact state, cross the placenta by simple diffusion and are governed by Fick’s Law of Diffusion. In general, hydrophobic compounds with a molecular weight of <500 Da can easily diffuse through the placenta. In the case of OTC analgesics, most compounds range between a molecular weight of 150 to 250 Da. Paracetamol for example has a molecular weight of 151.1 Da and can therefore readily diffuse across the placenta. It is a process that does not require an energy input as it utilizes the kinetic energy from these molecules and goes on until a concentration equilibrium is reached. A similar mechanism is used for the transport of NSAIDs. Paracetamol, aspirin and ibuprofen, being weak acids and lipid-soluble can all therefore cross the placental barrier and enter fetal circulation (Adams et al., 1969; Alano et al., 2001; Jacobson et al., 1991; Leverrier-Penna et al., 2018; Naga Rani et al., 1989; Shintaku et al., 2009; Siu et al., 2000; Weigand et al., 1984).

Some of the metabolites of analgesics are, however, substrates for drug transporters and can therefore be part of drug-drug interactions. For example, the transport of paracetamol metabolites is facilitated by ATP-binding cassette (ABC) transporters. More specifically, secretion of paracetamol-glucuronide relies on ABCC2, ABCC3 and ABCG2 membrane transporters, while paracetamol-sulphate can also be excreted via the ABCC4 transporter (Xiong et al., 2000, Xiong et al., 2002; Chen et al., 2003; Manautou et al., 2005; Zamek-Gliszczynski et al., 2005, Zamek-Gliszczynski et al., 2006a; Zamek-Gliszczynski et al., 2006b; Lee et al., 2009). ABCB1, ABCC1, ABCC4, ABCC5 and ABCG2 transporter expression was upregulated in patients after a toxic dose of paracetamol, suggesting that they might also play a role in paracetamol excretion (Barnes et al., 2007). In addition, cell line assays showed that paracetamol can interfere with solute carrier transporters (SLC),
mediating their excretion/uptake properties resulting in drug-drug interactions (Khamdang et al., 2002). As mentioned before, ibuprofen can diffuse through membranes without any transport proteins, but not much is known about specific transport of its metabolites. Both S- and R-ibuprofen enantiomers are, however, inhibitory substrates for SLC transporters, leading to drug-drug interactions (Khamdang et al., 2002; Itagaki et al., 2006; Chu et al., 2007; Omkvist et al., 2010; Honjo et al., 2011; Wang et al., 2012). Finally, aspirin metabolites are excreted by SLC22A6 and interact with SLC22A8 and ABCB1 transporters (Apiwattanakul et al., 1999; Kugai et al., 2013; Oh et al., 2014; Wang et al., 2014; Parvez et al., 2017).

Drug transporters in the placenta

Many drug-transporter proteins are expressed in the placental barrier and regulate fetal exposure to drugs and their substrates, by either blocking or facilitating transplacental transport (Iqbal et al., 2012; Walker et al., 2017). They are found on both apical (syncytiotrophoblast microvillus) and basal membranes, on the maternal and fetal side respectively (Figure 2), and have a large range of drug substrates (Table 2). They belong primarily to two super-families: the solute-linked carrier transporter proteins (SLC) and the ATP-dependent binding cassette transporter proteins (ABC) (Rubinchik-Stern and Eyal, 2012).

ABC transporters that have been detected in the human placenta are:

- phosphoglycoprotein (P-gp/ABCB1), breast cancer resistance protein (BCRP/ABCG2) and multidrug resistance-associated protein (MRP/ABCC)

transporters (Figure 2). ABCB1 transporter is located on the apical membrane of syncytiotrophoblasts throughout gestation, with even higher placental gene mRNA...
levels than liver and kidney in rats (Atkinson et al., 2003; Ceckova-Novotna et al., 2006; Cordon-Cardo et al., 1990; Leazer and Klaassen, 2003; Nagashige et al., 2003; St.-Pierre et al., 2000). ABCG2, similar to ABCB1, is also highly expressed on lipid rafts in the apical cell membrane of syncytiotrophoblasts (Litman et al., 2002; Mao, 2008; Szilagyi et al., 2017). Interestingly, apart from its drug transport properties in the placenta, ABCG2 facilitates trophoblast cell differentiation and survival. When ABCG2 is silenced in placenta cell cultures, higher rates of apoptosis occur, as well as changes in differentiation processes through β-hCG and HERV-W expression reduction (Evseenko et al., 2007).

ABCC1, 2, 3, 4 and 5 transporter proteins have also been localised on the surface of human placental syncytiotrophoblast cells. ABCC1 has been localised on both the apical and basal membranes of syncytiotrophoblasts in term placenta samples (Afrouzian et al., 2018; Nagashige et al., 2003; St.-Pierre et al., 2000). ABCC2 is located on the apical membrane of syncytiotrophoblasts and has over 30 known substrates, including paracetamol metabolites (Bakos et al., 2000; St.-Pierre et al., 2000; Meyer Zu Schwabedissen et al., 2005a). ABCC3 efflux transporter is also located on the apical membrane and its substrates include paracetamol metabolites (St.-Pierre et al., 2000; Azzaroli et al., 2007; Ni and Mao, 2011). ABCC4 transporter was found on the apical membrane, and facilitates efflux of some paracetamol metabolites as well (Ritter et al., 2005; Azzaroli et al., 2007; Russel et al., 2008). Finally, ABCC5 efflux transporter is found on the basal membrane of placental syncytiotrophoblast cells with a more modest list of substrates (Meyer zu Schwabedissen et al., 2005b).
SLC transporters in the human placenta include organic ion transporters and monoamine transporters (Figure 2). Organic cation transporters can either be potential-sensitive (OCTs) or proton gradient-driven (OCTNs). OCT3/SLC22A3 localises on the basal membrane of syncytiotrophoblast cells and is involved in the bidirectional transport of several cationic drugs and exogenous compounds including nicotine and amphetamine (Lee et al., 2018; Sata et al., 2005). OCTN1/SLC22A4 and OCTN2/SLC22A5 share very similar sequence homology and are both located on the apical membrane (Ganapathy and Prasad, 2005; Grigat et al., 2009; Grube et al., 2005). Two organic anion-transporting polypeptides (OATPs) are also found in the placenta, OATP2B1/SLCO2B1 and OATP4A1/SLCO4A1. SLCO2B1 influx transporter is found primarily on the basal membrane (Roth et al., 2012; St.-Pierre et al., 2000; Ugele et al., 2003). SLCO4A1 is another influx transporter that spans the apical membrane (Fujiwara et al., 2001; Tamai et al., 2000). Organic anion transporter 4 (OAT4/SLC22A11) is expressed in the basal membrane of human placental syncytiotrophoblasts and facilitates import of anionic drugs including some NSAIDs (Cha et al., 2000; Nigam et al., 2015; Noguchi et al., 2015; Rizwan and Burckhardt, 2007; Ugele et al., 2003).

OAT1/SLC22A6 efflux transporter is also expressed in human placenta; however, exact location was not specified (Hosoyamada et al., 1999). Although no literature was found that reported OAT3/SLC22A8 expression in human placenta, it has previously been detected in rat placenta (Leazer and Klaassen, 2003). Monoamine transporters in the placenta include the serotonin transporter (SERT/SLC6A4) and the norepinephrine transporter (NET/SLC6A5), both expressed on the apical membrane of syncytiotrophoblasts.
After a compound crosses the placenta, it reaches the fetal plasma and is distributed systemically. In general, placental blood is delivered to the fetal liver (where it provides 70% of the blood supply) and, through the ductus venosus and foramen ovale, straight to the heart, from where it is sent to the brain and upper extremities (Godfrey et al., 2012). It is thought that a similar distribution path is followed by the drugs that cross the placenta. Therefore, they can have a direct effect on these tissues.

**Drug metabolising enzymes in the placenta**

Before reaching the fetus, medications can be processed by the placental drug metabolising machinery, either posing risks for transport of toxic metabolites or having a potential protective effect through deactivation of toxic agents. The placenta contains enzymes that facilitate drug oxidation, reduction, hydrolysis, conjugation, glucuronidation, acetylation and sulfation and their activity varies with gestational age (Syme et al., 2004). Multiple cytochrome p450 (CYP) enzymes have been located within trophoblast cells of the placenta, namely CYP1A1, 3A4, 3A5, 3A7, 4B1, 19 (Myllynen et al., 2009). Several studies have detected mRNA and protein levels for these enzymes in first trimester and term placenta. Uridine 5'-diphospho-glucuronosyltransferases (UGTs), glutathione S-transferases (GSTs), one form of epoxide hydrolase, sulphotransferases and N-acetyltransferases mRNAs and proteins have also been found in the placenta representing metabolic phase II components. The expression levels and conformation of these enzymes in the placenta vary at different gestational stages (Rubinchik-Stern and Eyal, 2012). This metabolising activity of the placenta is another factor that controls xenochemical
transport from the mother to the fetus by regulating the quantity and make-up of metabolites (Pasanen, 1999).

OTC analgesics and their metabolites have known effects on the prostaglandin pathway (Anderson, 2008; Van Hecken et al., 2000; Lecomte et al., 1994). The placenta expresses components of the prostaglandin pathway, and expression patterns change with gestation and labour incidence and duration (Phillips et al., 2014). Therefore, placental analgesic pharmacodynamics may alter its physiological function and pregnancy progression.

Prenatal exposure and postnatal impacts

Medication use in pregnancy has been an issue of high controversy. The US Food and Drug Administration (FDA), after reviewing relevant studies, announced in 2015 that the evidence supporting association between analgesics and the development of ADHD in children is inconclusive (FDA, 2015). This was followed by a similar statement from the Society for Maternal-Fetal Medicine: Publications Committee in 2017, clearly stating that paracetamol is safe to use during pregnancy (SMFM (Society for Maternal-Fetal Medicine Publications Committee), 2017). A year later, a press release from the Royal College of Obstetricians and Gynaecologists further assured about the definite safety of paracetamol use during pregnancy and lactation, and suggested avoidance of NSAIDs unless clinically indicated (Bisson et al., 2018; RCOG, 2018). Finally, a recent statement from the European Medicines Agency based on recommendations from the Pharmacovigilance Risk Assessment Committee (PRAC), emphasises the inconclusive nature of evidence in the literature on in utero exposure to paracetamol (European Medicines Agency (EMA), 2019).

However, neither organisation cited all the relevant studies demonstrating the
potential adverse effects of analgesics *in utero* exposure to the offspring. Research on this topic is divided, and outcome associations should not be disregarded. Relevant literature is discussed below and summarised in Figure 3.

**Neurodevelopment**

Studies in various species have demonstrated risks in the use of analgesics during pregnancy with a focus on offspring neurodevelopmental disorders (Table 3). In mice, prenatal exposure to paracetamol disrupts brain development and behaviour (Hay-Schmidt *et al.*, 2017; Philippot *et al.*, 2017). More specifically, Hay-Schmidt and colleagues exposed mice *in utero* to paracetamol and its precursor aniline (from 7 days post coitum to delivery) and found decreased cell numbers in the hypothalamus which resulted in reduced sexual behaviour, territorial display and mating in male adults. Philippot and colleagues showed that paracetamol-exposure of mice during postnatal days 3 and 10 (correlates to 3rd trimester human development) led to changes in spontaneous behaviour and habituation decrease in a new home environment in adulthood, independent of sex. Another effect of large doses of paracetamol observed in neonatal rats (3rd trimester human development) was compromise of neurotransmission, spatial memory, social behaviour and motor function (Blecharz-Klin *et al.*, 2017); however, mice exposed to ibuprofen during the same developmental window showed no effect on behavioural pattern alterations (Philippot *et al.*, 2016). In humans, two studies in 2014 found an association between prenatal paracetamol exposure with ADHD-like and hyperkinetic behaviours in the resulting children at ages 7 and 11 years (Liew *et al.*, 2014; Thompson *et al.*, 2014). These findings are in agreement with Stergiakouli and colleagues in a longitudinal birth cohort study, reporting increased risks of multiple behavioural difficulties in the offspring after prenatal paracetamol exposure (Stergiakouli *et al.*, 2016). A
subsequent systematic review and meta-analysis, found an overall increased risk for ADHD, autism spectrum disorders (ASD) and hyperactivity symptoms in prenatally paracetamol exposed offspring (Masarwa et al., 2018). In another systematic review and meta-analysis of 8 studies, the authors found an overall increased risk of ADHD in the offspring following paracetamol exposure during pregnancy, with higher risk ratios when consumed during the 3rd trimester or for more than 28 days (Gou et al., 2019). Other studies in the past proposed an association between paracetamol, but not ibuprofen, use and increased risk of adverse neurodevelopmental outcomes in the offspring (Brandlistuen et al., 2013; Liew et al., 2016). Brandlistuen and colleagues, in a sibling-control analysis of the Norwegian Mother and Child Cohort Study, showed that prenatal paracetamol exposure for more than 28 days resulted in poor gross motor development, communication, externalising and internalising behavioural problems and higher activity levels in the offspring at 3 years of age (Brandlistuen et al., 2013). Liew et al. with their 2016 study following children and mothers from the Danish National Birth Cohort for more than a decade, found increased risk for ASD with hyperkinetic symptoms in children prenatally exposed to paracetamol (Liew et al., 2016). However, zebrafish model studies of developmental paracetamol exposure failed to show the same effect, clearly demonstrating the constraints of extrapolation to humans for this type of studies (Reuter et al., 2016). A prospective cohort study of 14,062 children reported adverse association of maternal paracetamol consumption during 18 to 32 pregnancy weeks and pre-school children behaviour (Golding et al., 2019). A study using the Swedish SELMA pregnancy cohort, showed a significant association between the detection of paracetamol and its metabolites in the urine of the mothers during pregnancy with language development delays in girls at 30 months of age (Bornehag et al., 2012; Bornehag et
al., 2018). Finally, a USA retrospective study showed an association between maternal consumption of paracetamol and aspirin during pregnancy to treat flu symptoms, and the incidence of neural tube defects in the offspring (Lynberg et al., 1994).

Increased risk for spastic cerebral palsy after paracetamol exposure during the second pregnancy trimester and bilateral spastic cerebral palsy after exposure to aspirin was reported in a large study including 185,617 mother-children pairs from a Danish and a Norwegian cohort (Petersen et al., 2018). However, another study did not find an association, which could be due to the inclusion of preterm and very preterm babies in their analyses (Marret et al., 2010). In contrast, another study including preterm babies reported an increased risk for cerebral palsy when the mother used NSAIDs during pregnancy (Tyler et al., 2012). A longitudinal prospective study in Seattle, USA, including 421 mother/offspring pairs, showed a dose-dependent decrease in intelligence quotient (IQ) levels and attention in 4-year old children exposed to aspirin during in utero development (Streissguth et al., 1987). This association was more pronounced in female than male offspring and was not significant for paracetamol exposure. However, one year later, a much larger cohort study assessing aspirin exposure during the first 20 weeks of pregnancy in 19,226 pregnancies, showed no association with adverse effects on offspring IQ (Klebanoff and Berendes, 1988). Finally, Associations between aspirin use during pregnancy and offspring psychotic episodes during adolescence have also been reported (Gunawardana et al., 2011).

Respiratory defects
Effects on the respiratory system following in utero exposure to OTC analgesics have also been reported (Table 4). A Norwegian study proposed a link between paracetamol use during pregnancy and the development of asthma in the offspring at year 3 and 7 (Magnus et al., 2016). The same study also showed positive association of asthma at 3 years of age with prenatal ibuprofen exposure. A longitudinal birth cohort study of 1,490 mother-child pairs showed associations between in utero exposure to paracetamol (but not ibuprofen) and risk of offspring recurrent wheeze and asthma in children between 3 and 5 years old (Sordillo et al., 2015). However, a previous prospective follow-up study of 1,505 women-children pairs considering paracetamol use during first and third trimesters and the emergence of wheeze or asthma in the offspring until year 6, did not find an increase in the risk (Kang et al., 2009). Subsequently, in a systematic review and meta-analysis, which also included the previous study, there was an overall significant association between paracetamol consumption during any trimester of pregnancy and childhood wheeze at the age of 2.5-7 years (Eyers et al., 2011). Other studies have similarly linked analgesics use during pregnancy with adverse effects on the respiratory system showing the emergence of wheeze at 1 and 5 years of age (Persky et al., 2008; Perzanowski et al., 2010).

Reproductive defects
A considerable effort has been focused on investigating the effects of OTC analgesics on the reproductive system, with a particular focus on male offspring due to their hypothesised androgen-disruptive effects (Table 5). Clinically relevant concentrations of analgesics have endocrine disrupting effects on the human fetal testis and alter germ cell biology (Ben Maamar et al., 2017; Mazaud-Guittot et al.,
Aspirin was shown to stimulate testosterone production and PGE$_2$ levels while inhibiting production of AMH, and paracetamol reduced IGF3, INSL3 and PGE$_2$ levels. A recent study in rats by Dean and colleagues revealed that *in utero* exposure to paracetamol and indomethacin resulted in DNA damage and reduced fetal germ cell number in both male and female offspring (Dean *et al*., 2016). The first study that reported an association between maternal analgesic consumption during pregnancy and offspring cryptorchidism was a nested case-control study of 6,699 singleton neonates (Berkowitz and Lapinski, 1996). In 2011, a prospective birth cohort study including 1,954 Danish and Finnish women, assessed OTC analgesics consumption during pregnancy (Kristensen *et al*., 2011). They found a dose-dependent positive association between concurrent use of analgesics use during the 2nd pregnancy trimester and cryptorchidism in male offspring; however, this association was reported only for the 491 women in their Danish cohort. Specific compounds significantly associated with cryptorchidism were aspirin and paracetamol. The authors also tested the effects of mild analgesics in rats and reported a correlation between prenatal exposure with shorter anogenital distance (AGD), and reduced testicular testosterone production in males. These findings agree with a UK prospective birth cohort follow-up study in 2016, which found that *in utero* paracetamol exposure during 8-14 gestation weeks was associated with a shorter AGD in human male infants (Fisher *et al*., 2016). Another retrospective cohort study in Denmark showed the same association after NSAIDs exposure (Lind *et al*., 2017). AGD is a known marker for hormonal disruption through androgen exposure with links to a variety of adverse reproductive outcomes such as cryptorchidism, hypospadias, sex development disorders, lower sperm quality, testicular function and lower testosterone levels (Thankamony *et al*., 2016). Risk for neonatal hypospadias
was found to be increased by the use of ibuprofen and aspirin (1st trimester) by two
further studies (Correy et al., 1991; Lind et al., 2013); however, other studies have
not found a significant association (Hernandez et al., 2012; Slone et al., 1976;
Snijder et al., 2012). In addition, experimental data from human fetal testes xenograft
into mice, showed reduced testicular testosterone production following prolonged
paracetamol exposure (Van Den Driesche et al., 2015). The concurrent use of
multiple analgesics in an ex vivo organotypic culture of fetal rat testis, showed
specific anti-androgenic effects by inhibiting testosterone production (Kristensen et
al., 2012). Another cohort study in the Netherlands reported that use of mild
analgesics during the second trimester of pregnancy resulted in a higher risk for
cryptorchidism, mainly associated with paracetamol use (Snijder et al., 2012). In
agreement with above findings, another large Danish cohort study in 2010 reported a
positive correlation between maternal paracetamol consumption during the first and
second trimesters and the incidence of cryptorchidism in the offspring (Jensen et al.,
2010). However, Philippat and colleagues did not find a significant correlation in their
cohort analysis (Philippat et al., 2011). Interestingly, a pre-conception cohort study,
has shown a relationship between adult male urinary paracetamol concentration and
reproductive function as higher concentration was associated with longer time to
pregnancy (Smarr et al., 2016).

Less is known about potential female-specific effects of in utero exposure to OTC
analgesics (Table 5). A study by Holm and colleagues in mice, reported reduced
follicular count in the ovaries of prenatally exposed female dams following
paracetamol exposure (Holm et al., 2016). In utero exposed females exhibited
significantly reduced fertility and premature ovarian insufficiency as adults. It has
been known for decades that paracetamol administration increases estradiol concentration in the plasma of adult women (Rogers et al., 1987), underlining a potential endocrine disruption in females similar to that in males. A recent Danish longitudinal cohort study found a positive correlation between in utero paracetamol exposure time, and earlier onset of pubertal events in the female offspring (Ernst et al., 2019). No significant association was observed in males. A recent study found a negative association between ibuprofen and ovarian cell proliferation and germ cell number, using first trimester human ovary ex vivo cultures (Leverrier-Penna et al., 2018). Similarly, another study exposing fetal ovarian cultures to paracetamol or ibuprofen found significant reduction in germ cell numbers (Hurtado-Gonzalez et al., 2018). The same study also tested exposure of these analgesics on fetal testes xenografted into mice and in-vitro culture, reporting similar results. Research on multiple species has shown adverse effects of aspirin and indomethacin on ovulation through prostaglandin disruption (Sirois et al., 2004). Pre-conception consumption of NSAID’s has also been associated with effects on implantation and reduced female fecundability (Mcinerney et al., 2017); however, peri-implantation use of aspirin was associated with increased fecundability (Jukic et al., 2020). Other findings in female adults include analgesic-induced disruption of menstruation and ovulation (Meyboom et al., 1995; Salman et al., 2015). Overall, more data is needed to understand the effects of analgesics on female reproductive ontogeny and function.

Cardiovascular defects

Paracetamol and NSAIDs are routinely used clinically to close patent ductus arteriosus in early postnatal life; however, less is known about specific effects of prenatal exposure (Table 6). A case series analysis concluded that there was a
causal relationship between maternal paracetamol use during pregnancy and fetal ductus arteriosus constriction/closure (Allegaert et al., 2019). The same association was observed earlier in a case report in 2015 following diclofenac use during the third trimester (Aker et al., 2015). This association was further confirmed by Tanaka and colleagues through their pharmacokinetic/pharmacodynamic prediction modelling, where the impact of paracetamol and NSAIDs on fetal ductus arteriosus constriction was successfully quantified (Tanaka et al., 2016). Significant association with cardiac defects was reported after use of NSAIDs during early pregnancy in a Swedish population study (Ericson and Källén, 2001). In addition, risk for pulmonary valve stenosis, hypoplastic cleft heart syndrome and tetralogy of Fallot was found to be higher in pregnancies with consumption of paracetamol compared to NSAIDs (Interrante et al., 2017).

Renal outcomes

In utero exposure to OTC analgesics have been associated with adverse effects on fetal urinary tract function (Table 7). A report of two cases of long-term exposure to diclofenac during pregnancy, proposed a causal relationship with fetal oligohydramnios during the second trimester, as the effect was reversible following discontinuation of use (Scherneck et al., 2015). An irreversible association of diclofenac with neonatal oliguria and renal failure in the offspring was described by a report of 3 cases (Phadke et al., 2012). On the other hand, a clinical trial reported no effect of low-dose aspirin to neither offspring amniotic fluid volume nor fetal urine output (Maher et al., 1993). Paracetamol exposure during the third trimester was also not found to have a significant association with fetal renal toxicity in a prospective cohort study (Dathe et al., 2019).
Other perinatal outcomes

Adverse effects on the offspring at birth have also been associated with *in utero* analgesics exposure (Table 8). A study by Werler and colleagues demonstrated a significant association between paracetamol use during the first trimester of pregnancy and the development of amniotic band defects (Werler *et al.*, 2003). In another case-control study by the same group, gastroschisis was associated with paracetamol and aspirin use during early pregnancy and was independent from maternal symptoms (Werler *et al.*, 2002). An increased risk for gastroschisis was also reported in infants after aspirin exposure during the first trimester of pregnancy in a meta-analysis of the literature (Kozer *et al.*, 2002). These results were in agreement with a previous study by Torfs and colleagues, associating aspirin and ibuprofen (but not paracetamol) consumption during pregnancy with increased risk for gastroschisis (Torfs *et al.*, 1996). Conversely, diclofenac use during the first was not found to have a significant association with major birth defects (Cassina *et al.*, 2010; Padberg *et al.*, 2018). Similar results were also reported for use of multiple NSAIDs during the first 12 weeks of gestation where no association with major birth defects in the offspring was found (van Gelder *et al.*, 2011). A USA cohort study comparing the incidence of birth defects between the use of NSAIDs and paracetamol, showed that NSAID consumption during pregnancy can result in higher risk for gastroschisis, hypospadias, cleft palate, cleft lip, anencephaly and spina bifida than paracetamol in-utero exposure (Interrante *et al.*, 2017). On the other hand, two studies reporting 60 and 300 cases of paracetamol overdose during pregnancy, did not show strong associations with fetal toxicity or other adverse outcomes (Riggs *et al.*, 1989; McElhatton *et al.*, 1997). It should be noted that these
women were treated for overdoses with N-acetylcysteine, ipecac or methionine.

Finally, no association was observed with paracetamol use and general fetal growth during pregnancy in a prospective cohort study including 2,291 women (Smarr et al., 2019).

Pregnancy outcome

Considerable effort has been focussed on pregnancy-specific outcomes following OTC exposure (Table 9). A case-control study in Denmark reported an increased risk of miscarriage after the use of NSAIDs during pregnancy, with the highest risk when consumed 1 week before the miscarriage (Nielsen et al., 2001). Two years later, another cohort study in San Francisco, USA, provided similar findings, with a higher risk of miscarriage reported following prenatal exposure to NSAIDs and aspirin, however, not paracetamol (Li et al., 2003). In contrast, a cohort study in Germany did not find any significant association between ibuprofen exposure during the first trimester and major birth defects in the offspring or spontaneous abortion rates (Dathe et al., 2018). The same results were observed in another German study using the same cohort, but considering diclofenac use during pregnancy (Padberg et al., 2018). Spontaneous abortion was also not significantly associated with multiple NSAID consumption either during pregnancy or periconceptional in two further cohort studies (Daniel et al., 2014; Edwards et al., 2012). In addition, when considering aspirin only, a meta-analysis of randomised controlled studies showed no significant association with miscarriage rates (Kozer et al., 2003). A positive association was however reported by a case-control study considering multiple NSAIDs and spontaneous abortion risk (Nakahai-Pour et al., 2011). Finally, a retrospective cohort study, also in Germany, showed that maternal paracetamol
intake during the third trimester of pregnancy was positively associated with lower numbers of hematopoietic stem cells in cord blood (Bremer et al., 2017).

Discussion

There is a high prevalence of self-medication during pregnancy, which increases annually (Mosley et al., 2015; Van Calsteren et al., 2016). Our review of the current literature revealed that pregnant women of the Western world are using OTC medications more frequently. This observation is in agreement with previous findings of Baraka and colleagues in their multi-ethnicity cohort of pregnant women (Baraka et al., 2013). In utero exposure is therefore ubiquitous. OTC medication abundance, ease of access, low cost, limited dose and side-effects awareness, general Western lifestyle, improper record keeping and frequent lack of adequate advice from healthcare professionals, make this exposure hard to quantify. This results in a series of studies basing their findings on data that may not be accurate, and suffer from different types of bias. Several OTC medications meant for other purposes can also contain doses of analgesics (e.g. cold and flu remedies), and simultaneous consumption might therefore have synergistic effects or lead to surpass of recommended doses. In addition to drug consumption, environmental influences can also play an important role, for example aniline. This compound is an industrial chemical that can be found in the air, water, dietary products and synthetic products such as rubbers, dyes, pesticides, diphenylamine or synthetic fibres. Aniline is rapidly converted into paracetamol by the human liver (Holm et al., 2015). Therefore, in-utero exposure may not only be limited to maternal consumption of the analgesic, complicating exposure analysis studies further. The potential for other pharmaceuticals or environmental endocrine disruptor mixtures to modulate effects

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of analgesics could also be true, but this has not been explored by human studies to date.

Many analgesics freely cross the placenta and reach the developing fetus. We know this occurs mostly by measurements of the compounds and their metabolites in fetal plasma/meconium/amniotic fluid. Something that is still not fully understood is whether all metabolites have the ability to cross the placenta to the same degree, at the same speed and which of them might be responsible for the observed adverse outcomes in the offspring for each compound. In Figure 4 we summarise a hypothesis of all the possible routes that could connect maternal consumption to postnatal ill health. Whether one, a combination, or all could be correct requires further research. This hypothesis can be relevant to any type of medication or combination of different compounds. As shown by many of the cited studies, during the course of their pregnancy, women often use more than one compound either at different times or in combination. Combining different analgesics or exceeding recommended doses can sometimes be unintentional as many of these agents are included in other medications that are also available OTC. Mixing different analgesics together, even though it can be part of a therapeutic regimen for certain indications such as severe pain, can also lead to drug interactions with substantial health risks (Mark et al., 2008). Inevitably, when it comes to OTC medications, this risk is elevated. The combination of analgesic compounds in pregnancy can therefore put the fetus at risk for toxicity, leading to adverse health outcomes that may be a result of two or more exposures. Almost certainly, whether due to exposure to one or multiple compounds, different fetal organ systems will be affected via different pathways and mechanisms, and possibly at different levels of exposure.
On the other hand, fetal programming can occur by alterations in the placenta alone through exposure (Kratimenos and Penn, 2019). Therefore, another potential hypothesis might be that accumulation of OTC compounds in the placenta can indirectly result in fetal programming via alterations in placental function. Gädeke first described in the early 70’s what is now general knowledge, that xenobiotic metabolism is altered with life stage (age), with fetuses and neonates being more susceptible than adults (Gädeke, 1972; Allegaert et al., 2008). The basis of this observation could be alterations in pharmacokinetics and pharmacodynamics between different gestational stages resulting from a different drug metabolising enzyme expression profile. In addition, adult drug metabolism is sexually dimorphic, which is something that is likely to also be true during fetal life. This aspect is overlooked by the majority of current literature and pharmaceutical companies. Therefore, toxicity of metabolites might be completely different considering the altered pharmacodynamics/pharmacokinetics of drug compounds during pregnancy and fetal life/sex and the lack of adequate knowledge to understand drug metabolism at this developmental stage.

The liver, kidney and intestine are the major organs that metabolise paracetamol and NSAIDs in the adult. However, all organ systems have at least mild metabolic activity. For instance paracetamol is oxidised to NAPQI by rat brain cells in situ (Howard et al., 2003). Drug metabolising enzymes are also expressed in adrenals, lungs, heart, ovaries, testes, prostate, skin and placenta (Xinxin and Laurence, 2003; Du et al., 2006; Biéche et al., 2007). Reviewed literature presented here, suggests neurodisruptive and endocrine disruptive properties of in utero exposure to analgesics. The higher frequency of male reproductive outcomes so far reported
could be explained by sex-specific endocrine disruption and/or abnormal androgen
docrinology during fetal life.

Another plausible explanation for the adverse effects of analgesics could be via their
association with prostaglandins. Prostaglandins are important components for
pregnancy and parturition as they stimulate uterine contractions and enhance
cervical ripening. NSAIDs inhibit cyclo-oxygenase (COX) enzymes and therefore
downregulate prostaglandin synthesis and prolong gestation and labour. Premature
labour can be successfully prevented using ibuprofen, aspirin, diclofenac and
ketoprofen, all available over-the-counter (Dawood, 1993; Lewis and Schulman,
1973). These properties could therefore explain the observed associations of their
use during pregnancy and miscarriage. Prostaglandins are also important regulators
of embryonic and fetal reproductive development as demonstrated in mice models
(Gupta, 1989; Gupta and Goldman, 1986). Inhibition of the prostaglandin pathway
during gestation can therefore also interact with human fetal reproductive system
development, leading to the observed neonatal reproductive outcomes. Despite their
well-understood functions, little information is available about COX enzyme
expression and role during fetal life. A rat study showed their expression in fetal skin,
cartilage, brain, heart and kidney (Stanfield et al., 2003), while experiments using
transgenic mice demonstrated the importance of COX2 in normal fetal development
(Shim et al., 2010). Reported outcomes of in utero exposure could therefore be due
to tissue-specific inhibition of COX enzymes, possibly dependant on gestation,
quantity and frequency of exposure.
Pharmacokinetics and pharmacodynamics are altered during pregnancy through a series of physiological changes (Loebstein et al., 1997; Sen et al., 1998). These changes should be considered by physicians for adjustments in drug dosage and frequency during this time to ensure the safety of the mother, which is unfortunately very difficult in practice (Costantine, 2014). In the context of analgesics, there is significant increase in paracetamol clearance during pregnancy, leading to a faster decrease of its therapeutic effects. However, in an attempt to increase efficacy, higher doses could lead to a proportional increase in oxidation into toxic metabolites (Allegaert and van den Anker, 2017). There is no study, to our knowledge, investigating differential pregnancy dosing of analgesics. Nevertheless, in the single systematic review on the topic, the authors reported significant pharmacokinetic changes between pregnant and non-pregnant women for paracetamol, emphasizing the need for further research to address the need for drug optimisation for pregnancy (Pariente et al., 2016).

Disturbed prenatal programming can, therefore, occur through either fetal tissue toxicity by the accumulation of toxic metabolites or disruption of physiological processes and normal development through the inhibition of prostaglandin synthesis. Considering the current literature, no definite conclusions can be drawn. Although results from many studies are consistent, interpretations should be made with caution and future studies should pursue this important set of associations with further research. We cannot say confidently that OTC analgesics are indeed a direct cause of all observed offspring outcomes. All discussed research demonstrates the challenges of conducting this type of exposure studies, exemplifies the difficulty of accounting for other unmeasured environmental influences and genetics, and
underlines the need of follow-up studies on larger cohorts considering a wider time window. Precise assessment of exposure including dose, timing and duration of use during pregnancy is what is mostly missing from current literature and should be included in designing future studies. Parallel research on the effects of the underlying maternal conditions that require analgesics consumption should also rule out whether associations are indeed a matter of analgesics exposure or a result of physiological response/adaptation to maternal health status.

Another hurdle to definitive decision making is that most studies looking into OTC analgesic exposure during pregnancy might suffer from confounding of their results by indication for use. While many results for the same compound are consistent between studies in large cohorts, underlying acute or chronic maternal health conditions are overlooked by the majority. This is a very important point for consideration in the design of future studies, however, it is challenging to tackle due to the difficulty of accurate quantification of data on such high prevalence of consumption and subjective decision-making by the mothers.

More data focusing on specific pregnancy timing of consumption are needed to identify developmental windows of sensitivity for different compounds and the associated offspring outcomes. Information on analgesic consumption during very early pregnancy should also be collected from pre-pregnancy cohorts, as analgesic use before and while trying to conceive could then be assessed and tracked more easily after the pregnancy is known. Few prospective pregnancy cohorts are currently available (e.g. EARTH, Messerliem et al., 2018, and ALSPAC, Lawlor et al., 2019); however, to the best of our knowledge, there is no published literature
concerning OTC analgesics use in these cohorts. Research including multiple
exposure models would shed light into gene-environment and immune-environment
interactions. In addition, focus should be given into research to elucidate the
underlying mechanisms and develop safer analgesics. Over two decades ago,
designing a study that includes human fetal samples appeared impossible, directing
the field towards live animal models for in vivo studies (Ring et al., 1999). We are
now able to obtain valuable fresh tissue samples from human fetuses coming from
elective pregnancy terminations. These tissues can be analysed morphologically and
used for genomics/proteomics and culture investigations, with a focus on gestational
stage/s of exposure and fetal sex (Hurtado-Gonzalez et al., 2018). While more
research is needed, current technological and practical tools make real progress in
understanding gestation risks of analgesics and other drugs more likely than ever
before.

Even though literature evidence considering different offspring outcomes following in
utero analgesics exposure is conflicting, the presence of studies showing definite
associations should not be overlooked. Pain and fever management during
pregnancy should always be considered, but health risks versus benefits for both the
mother and the fetus must be considered. One realistic approach is caution against
their indiscriminate use to ensure the minimum effective dose is administered for the
shortest possible time. Given their routine use, OTC analgesic consumption during
pregnancy requires further in-depth study so that the public health implications are
understood and the potential negative effects are minimised.

**Author’s roles**
P.A.F. proposed the work. A.Z. conducted the literature search and prepared the manuscript, figures and tables. All authors contributed to critical discussion, development and review of the final manuscript.

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**Conflict of interest**

None of the authors has any conflict of interest to declare.

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Figure Legends

Figure 1. Prevalence of analgesics consumption during pregnancy from different parts of the world. Percentages summarised here as reported by the literature. More details on each study can be found in Table 1 and in text.

Figure 2. Schematic diagram of the major drug transporters on human placental syncytiotrophoblast and their substrates according to medication type. Solute-linked carrier (SLC) (blue) and adenosine triphosphate binding cassette (ABC) transporters (red). Phase I metabolising enzymes (P1); phase II metabolising enzymes (P2). Arrow direction demonstrates influx/efflux. Note that not all substrates have been examined in the human placenta. Figure was prepared based on information cited in this review. * exact placental membrane localisation not known; † localised on both membranes.

Figure 3. OTC analgesic exposures during pregnancy and their associations with adverse offspring health outcomes from current literature. Indication of references according to study type: * Cohort Studies, § Case-control/Case Report Studies, ¥ Systematic reviews/Meta-analyses, † Experimental Studies.

Figure 4. Hypothesis of different routes of analgesics and their metabolites during pregnancy.