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

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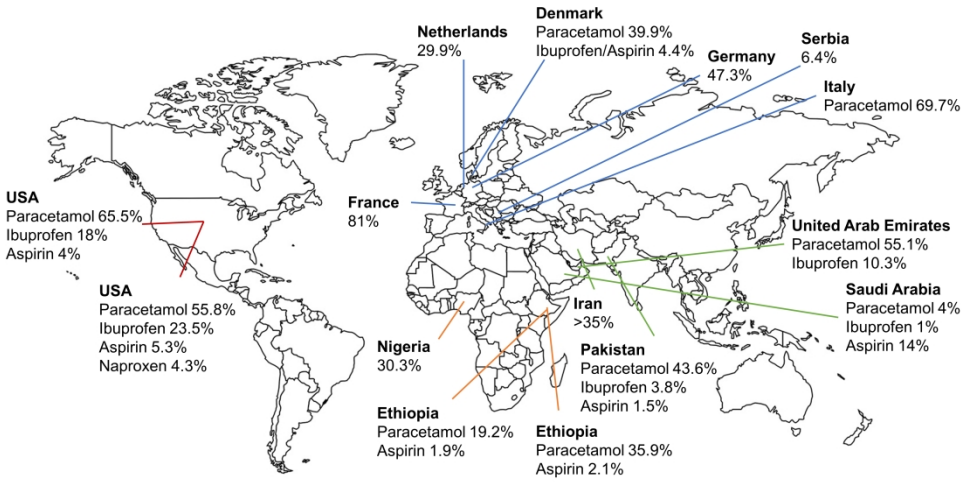

Figure 1. Prevalence of analgesics consumption during pregnancy from different parts of the world. Percentages summarised here as reported by the literature. More details on each study can be found in Table 1 and in text.

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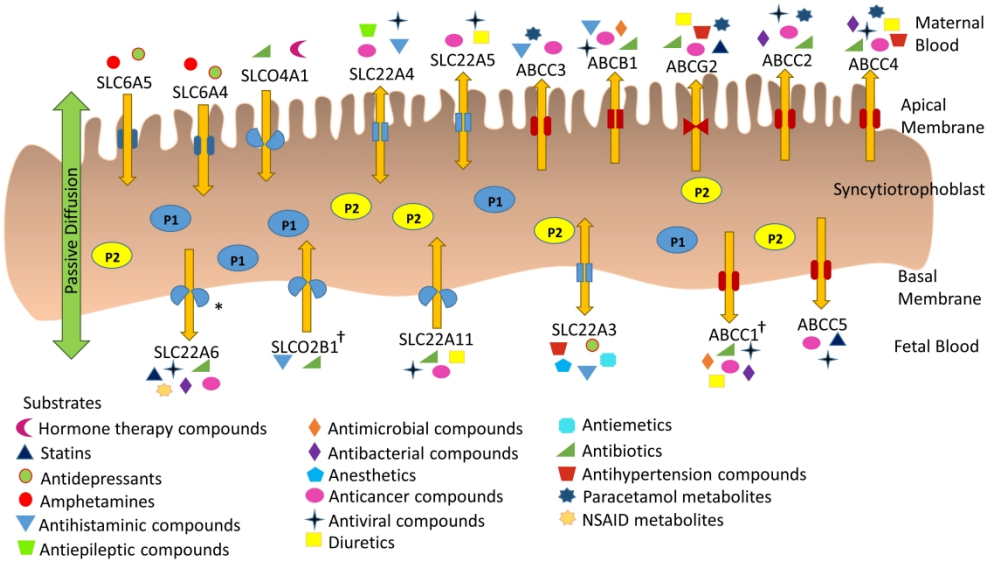

Figure 2. Schematic diagram of the major drug transporters on human placental syncytiotrophoblast and their substrates according to medication type. Solute-linked carrier (SLC) (blue) and adenosine triphosphate binding cassette (ABC) transporters (red). Phase I metabolising enzymes (P1); phase II metabolising 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

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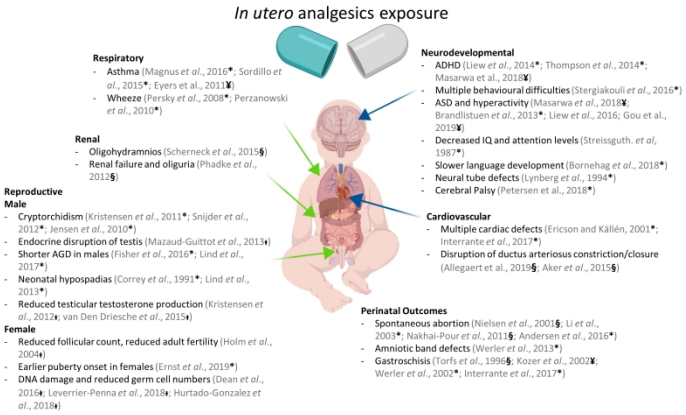

Figure 3. OTC analgesic exposures during pregnancy and their associations with adverse offspring health outcomes from current literature. Indication of references according to study type: * Cohort Studies, § Case-control/Case Report Studies, ¥ Systematic reviews/Meta-analyses, † Experimental Studies

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Table 1. Proportion of women using analgesics during pregnancy. Data from various studies across global regions.

	Country	Study Period	Gestational Period	Cohort size (n)	Data collection method	Analgesics use (%)	OTC Analgesics	Study
Europe	Denmark	2010-2012	1st and 2nd trimester	1,027	Questionnaires	39.9 4.4	Paracetamol Ibuprofen/Aspirin	Lind *et al.*, 2017
	Netherlands	2002-2006	All trimesters	3,184	Questionnaires	29.9	Paracetamol other	Snijder *et.al.*, 2012
	Germany	2011-not specified	All trimesters	518	Questionnaire-assisted interviews	47.3	Paracetamol NSAIDs Aspirin	Bremer *et al.*, 2017
	France	2003-2006	1st and 2nd trimester	895	Questionnaires	81	Paracetamol Ibuprofen Aspirin	Philippat *et al.*, 2011
	Italy	2016-2017	All trimesters	503	Questionnaires	69.7	Paracetamol	Navaro *et al.*, 2018
	Serbia	2009-2010	1st and 2nd trimester	311	Questionnaires	6.4	Paracetamol	Odalovic *et al.*, 2012
	UK	1991-1992	1st trimester 2nd trimester 3rd trimester	14,119	Questionnaires	39.6 39.2 30.9	General analgesics (Paracetamol most common)	Headley *et al.*, 2004
Australia, Europe, America	Europe, Australia, America	2011-2012	All trimesters	9,459	Online questionnaires	47.7 4.5 0.6	Paracetamol NSAIDs Aspirin	Lupattelli *et al.*, 2014
	USA	1998-2005	All trimesters	10,533	Interviews	65.5 18 4	Paracetamol Ibuprofen Aspirin	Werler *et al.*, 2005
	USA	2004-2009	1st trimester	5,381	Interviews	55.8 23.5 5.3 4.3	Paracetamol Ibuprofen Aspirin Naproxen	Thorpe *et al.*, 2013
	USA (Hispanic population)	Not specified	Did not ascertain	485	Questionnaires	13 4 3	Paracetamol Ibuprofen Aspirin	Bercaw *et al.*, 2010
Middle East	United Arab Emirates	October to December 2016	"varying" trimesters	140	Questionnaires	55.1 10.3	Paracetamol Ibuprofen	Abduelkarem & Mustafa, 2017
	Saudi Arabia	April and May 2017	All trimesters	100	Questionnaires	14 4 1	Aspirin Paracetamol Ibuprofen	Al Bahhawi *et al.*, 2018
	Iran	Not specified	Not specified	180	Questionnaires	>35	General OTC medication	Baghianimoghadam *et al.*, 2013

	Pakistan	April to October 2014	All trimesters	351	Interviews	43.6 1.5 3.8	Paracetamol Aspirin Ibuprofen	Bohio *et al.*, 2016
Africa	Ethiopia	February to March 2012	All trimesters	339	Patient records and interviews	35.9 2.1	Paracetamol Aspirin	Mohammed *et al.*, 2013
	Ethiopia	June to August 2007	All trimesters	1,268	Interviews	19.2 1.9	Paracetamol Aspirin	Kebede *et al.*, 2009
	Nigeria	Not specified	All trimesters	518	Questionnaires	30.3	Not specified	Abasiubong *et al.*, 2012

Table 2. Drug transporters localised on human placenta and their known substrates

			Substrates		
Transporter	**Placenta membrane localisation**	**Direction of transport**	**OTC analgesics**	**Others**	**Reference**
ABCB1	Apical	Efflux	Aspirin metabolites	Anticancer drugs, antibiotics, HIV protease inhibitors, morphine	(Kim, 2002)
ABCG2	Apical	Efflux	Paracetamol metabolites	Chemotherapeutic agents, antiretroviral medications, antibiotics, glyburide (hypoglycemic agent)	(Mao and Unadkat, 2015)
ABCC1	Apical and basal	Efflux		Antibiotics, antimicrobial agents, Hepatitis Bi inhibitors, HIV inhibitos, anticancer medications	(Renes *et al.*, 1999; Olson *et al.*, 2002)
ABCC2	Apical	Efflux	Paracetamol metabolites	Antibiotics, antineoplastic compounds, antibacterial agents, AIDS inhibitors, HIV inhibitors	(Bakos *et al.*, 2000; St-Pierre *et al.*, 2000; Grube *et al.*, 2005; Meyer Zu Schwabedissen *et al.*, 2005)
ABCC3	Apical	Efflux	Paracetamol metabolites	Antihistaminic agents, antineoplastic compounds	(St-Pierre *et al.*, 2000; Azzaroli *et al.*, 2007; Ni and Mao, 2011)
ABCC4	Apical	Efflux	Paracetamol metabolites	Antibacterial agents, antiviral agents, antihypertenstion agents, diuretic medications	(Ritter *et al.*, 2005; Azzaroli *et al.*, 2007; Russel, Koenderink and Masereeuw, 2008)
ABCC5	Basal	Efflux		Antineoplastic agents, Hepatitis B inhibitors, statins	(Meyer zu Schwabedissen *et al.*, 2005)

OCT3/SLC22A3	Basal	bidirectional		Cationic drugs, nicotine, amphetamine	(Sata *et al.*, 2005; Lee *et al.*, 2018)
OCTN1/SLC22A4	Apical	bidirectional		Respiratory agents, anti-viral compounds, anti-cancer drugs	(Koepsell, 2004; Nakamura *et al.*, 2010; Mukherjee *et al.*, 2013; Yang *et al.*, 2016)
OCTN2/SLC22A5	Apical	bidirectional		Respiratory agents, anti-viral compounds, anti-cancer drugs	(Ohashi *et al.*, 1999; Koepsell, 2004; Nakamura *et al.*, 2010; Mukherjee *et al.*, 2013; Yang *et al.*, 2016)
OATP2B1/SLCO2B1	Basal	Influx		Aliskiren, atorvastin, benzylpenicillin	(St-Pierre *et al.*, 2000; Ugele *et al.*, 2003; Roth, Obaidat and Hagenbuch, 2012)
OATP4A1/SLCO4A1	Apical	Influx		Benzylpenicillin, thyroxine (T4), triiodothyronine (T3)	(Tamai *et al.*, 2000; Fujiwara *et al.*, 2001)
OAT4/SLC22A11	Basal	Influx	NSAIDs	Antihypertensive compounds	(Cha *et al.*, 2000; Ugele *et al.*, 2003; Rizwan and Burckhardt, 2007; Nigam *et al.*, 2015; Noguchi *et al.*, 2015)
OAT1/SLC22A6	Not known	Efflux	Aspirin metabolites	Antiviral agents, antibacterial agents, anticancer drugs, statins, antibiotics	(Rizwan and Burckhardt, 2007; Reese *et al.*, 2016)
SERT/SLC6A4	Apical	Influx		Amphetamines, amphetamine derivatives, antidepressants, ADHD medication (atomoxetine)	(Madras *et al.*, 2005; Velasquez *et al.*, 2013)

NET/SLC6A5	Apical	Influx	Amphetamines, amphetamine derivatives, antidepressants, ADHD medication (atomoxetine)	(Madras *et al.*, 2005; Velasquez *et al.*, 2013)

Table 3. Studies on neurodevelopmental offspring outcomes following *in utero* exposure to OTC analgesics

Study details						**Results**	
Outcome Category	**Analgesic**	**Study time**	**Study type**	**Cohort**	**Data collection method**	**Main study results**	**Study**
Neurodevelopment							
	Paracetamol	1996-2002	Prospective cohort study	64,322 participants	Telephone interviews	Higher risk for ADHD-like behaviours and HKDs in children	(Liew *et al.*, 2014)
	Paracetamol	1995-1997	Prospective follow-up cohort study	871 participants	Questionnaires, parent reports of children ADHD symptoms	Higher risk for ADHD at 7 and 11 years of age	(Thompson *et al.*, 2014)
	Paracetamol	1991-1992	Prospective cohort study	7,796 participants	Questionnaires	Higher risk for multiple behavioural difficulties	(Stergiakouli *et al.*, 2016)
	Paracetamol	Included studies up to January 2017	Systematic review, meta-analysis and meta-regression analysis	132,738 participants from 7 cohort studies	Searches in MEDLINE, Embase and Cochrane databases	Higher risk for ADHD, ASD and hyperactivity symptoms	(Masarwa *et al.*, 2018)
	Paracetamol	Included studies up to November 2018	Systematic review and meta-analysis	244,940 participants from 8 cohort studies	Searches in PubMed, Embase, Web of Science and Cochrane databases	Higher risk for ADHD	(Gou *et al.*, 2019)
	Paracetamol	1999-2008	Sibling-controlled cohort study	48,631 participants	Questionnaires	Higher risk for adverse neurodevelopmental outcomes at the age of 3 years	(Brandlistuen *et al.*, 2013)

	Paracetamol	1996-2002	Prospective cohort study	64,322 participants	Telephone interviews	Higher risk for ASD with hyperkinetic symptoms	(Liew *et al.*, 2016)
	Paracetamol	1991-1992	Prospective cohort study	14,062 participants	Questionnaires	Adverse association with pre-school children behaviour	(Golding *et al.*, 2019)
	Paracetamol	2007-2010	Population-based prospective study	754 participants	Maternal reports and paracetamol urinary concentration measurements	Significant association with language delay in girls at 30 months of age	(Bornehag *et al.*, 2018)
	Paracetamol, aspirin	1996-2002 1999-2008 (two cohorts)	Prospective cohort study	185,617 participants	Questionnaires and telephone interviews	Higher risk for spastic CP	(Petersen *et al.*, 2018)
	Paracetamol, aspirin	1974-1975	Prospective cohort study	421 participants	Interviews and laboratory examinations of children	Decrease in IQ levels at 4 years of age after maternal consumption of aspirin during pregnancy	(Streissguth *et al.*, 1987)
	Paracetamol, aspirin	1968-1980	Retrospective population-based case control study	385 infants with NTD and 2,676 control infants	Interviews	Increased incidence of NTDs when consumed to treat flu symptoms	(Lynberg *et al.*, 1994)
	Aspirin	1997	Retrospective cohort study	656 participants	Questionnaires	No association between low-dose aspirin consumption and adverse offspring neurodevelopmental	(Marret *et al.*, 2010)

						outcomes in preterm babies	
	Aspirin	1959-1966	Prospective cohort study	19,226 participants	Interviews and follow-up examinations of children	No association with decreased IQ levels at 4 years of age	(Klebanoff and Berendes, 1988)
	Aspirin	1991-1992	Longitudinal cohort study	6,437 participants	Questionnaires	Increased risk of offspring psychotic experiences during adolescence	(Gunawardana *et al.*, 2011)
	NSAIDs, aspirin	2002-2004	Prospective cohort study	877 participants	Interviews	Increased risk of preterm infants developing CP	(Tyler *et al.*, 2012)

Table 4. Studies on respiratory offspring outcomes following *in utero* exposure to OTC analgesics

Study details						Results	
Outcome Category	**Analgesic**	**Study time**	**Study type**	**Cohort**	**Data collection method**	**Main study results**	**Study**
Respiratory							
	Paracetamol, ibuprofen	1999-2008	Prospective cohort study	53,169 participants	Questionnaires	Paracetamol: Higher risk for asthma development at 3 and 7 years of age Iburofen: Higher risk for asthma development at 3 years of age	(Magnus *et al.*, 2016)
	Paracetamol	1999-2002	Prospective cohort study	1,490 participants	Interviews and questionnaires	Higher risk for recurrent wheeze and asthma between 3 and 5 years of age	(Sordillo *et al.*, 2015)
	Paracetamol	1997-2009	Prospective cohort study	1,505 participants	Interviews	No association with increased asthma in children	(Kang *et al.*, 2009)
	Paracetamol	Included studies up to 2010	Systematic review and meta-analysis	6 studies	Searches in Medline, EMBASE, Cochrane and Cochrane Database of Systematic Reviews	Increased risk for wheeze in children between 2.5 and 7 years of age	(Eyers *et al.*, 2011)

	Paracetamol	Not specified	Randomised controlled trial	345 participants	Questionnaires	Higher risk for wheeze during the 1st year of age	(Persky *et al.*, 2008)
	Paracetamol	1998-2006	Prospective cohort study	301 participants	Questionnaires	Association of use during middle and late pregnancy with offspring wheeze at 5 years of age	(Perzanowski *et al.*, 2010)

Table 5. Studies on reproductive offspring outcomes (male and female) following *in utero* exposure to OTC analgesics

Study details						**Results**	
Outcome Category	**Analgesic**	**Study time**	**Study type**	**Cohort**	**Data collection method**	**Main study results**	**Study**
Reproductive							
Testes	Ibuprofen	n/a	*Ex-vivo* and xenograft systems	First and second trimester human fetal testes	n/a	Altered germ cell biology and had endocrine disrupting effects on first trimester testes	(Ben Maamar *et al.*, 2017)
	Paracetamol, aspirin	n/a	*Ex-vivo* system	First trimester human fetal testes	n/a	Endocrine disrupting effects on first trimester testes	(Mazaud-Guittot *et al.*, 2013)
	Exact compound not specified	1987-1990	Nested case-control study	6,699 male neonates	Questionnaires and examinations for cryptorchidism	Higher risk for cryptorchidism following analgesic consumption during pregnancy	(Berkowitz and Lapinski, 1996)
	Paracetamol, aspirin	Not specified	Prospective cohort study	1,954 participants	Questionnaires and interviews	Dose-dependent higher risk for cryptorchidism	(Kristensen *et al.*, 2011)
	Paracetamol	2001-2009	Prospective cohort study	343 participants	Questionnaires	Exposure during 8-14 weeks was associated with shorter AGD	(Fisher *et al.*, 2016)
	Paracetamol, NSAIDs	2010-2012	Prospective birth cohort study	1,027 participants	Interviews and examinations	Shorter AGD after analgesic exposure, especially	(Lind *et al.*, 2017)

						simultaneous use of paracetamol with NSAIDs	
	Aspirin	1982-1989	Prospective survey	56,037 participants	Forms completed by the doctor	Higher risk for hypospadias when consumed during the 1st trimester	(Correy *et al.*, 1991)
	Ibuprofen	1977-2007	Case-control study	1,537 infants with hypospadias 4,314 controls	Interviews	Higher risk for hypospadias	(Lind *et al.*, 2013)
	NSAIDs	1997-2005	Case-control study	14,915 birth defect cases 5,546 controls	Interviews	No significant association with hypospadias	(Hernandez *et al.*, 2012)
	Aspirin	Not specified	Retrospective cohort study	50,282 participants	Interviews and reviews of clinical records	No significant association with hypospadias	(Slone *et al.*, 1976)
	Paracetamol	2002-2006	Prospective cohort study	3,184 participants	Physical examinations, questionnaires, interviews and biological samples	Higher risk for cryptorchidism when consumed in the 2nd trimester No association with hypospadias	(Snijder *et al.*, 2012)
	Paracetamol	n/a	Xenograft system	14 human fetal testes	n/a	Reduced testicular testosterone production	(Van Den Driesche *et al.*, 2015)
	Paracetamol	1996-2002	Retrospective cohort study	47,400 participants	Interviews and questionnaires	Higher risk for cryptorchidism	(Jensen *et al.*, 2010)

						when used for more than 4 weeks during the 1st and 2nd trimester	
	Paracetamol, Aspirin, ibuprofen	2003-2006	Retrospective cohort sudy	903 participants	Questionnaires	No significant association with cryptorchidism	(Philippat *et al.*, 2011)
Ovaries	Ibuprofen	n/a	*Ex-vivo* system	185 human fetal ovaries	n/a	Effect on ovarian cell proliferation and germ cell number during the 1st trimester	(Leverrier-Penna *et al.*, 2018)
	Paracetamol, ibuprofen	n/a	*Ex-vivo* system	3 human fetal ovaries	n/a	Significant reduction in ovarian germ cell number	(Hurtado-Gonzalez *et al.*, 2018)
	Paracetamol	2012-2017	Longitudinal cohort study	15,822 participants	Interviews and questionnaires	Earlier onset of pubertal events in female offspring	(Ernst *et al.*, 2019)

Table 6. Studies on cardiovascular offspring outcomes following *in utero* exposure to OTC analgesics

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

Table 7. Studies on renal offspring outcomes following *in utero* exposure to OTC analgesics

Study details						Results	
Outcome Category	**Analgesic**	**Study time**	**Study type**	**Cohort**	**Data collection method**	**Main study results**	**Study**
Renal							
	Diclofenac	Not specified	Case report	2 cases	Case description	Oligohydramnios on both cases during the 2nd trimester	(Scherneck *et al.*, 2015)
	Diclofenac	Not specified	Case report	3 cases	Case description	Irreversible association with neonatal renal failure and oliguria	(Phadke *et al.*, 2012)
	Aspirin	1991-1992	Clinical trial	32 aspirin-treated 27 placebo-treated participants	n/a	No significant association of low-dose aspirin with amniotic fluid volume or fetal urine output	(Maher *et al.*, 1993)
	Paracetamol	2008-2019	Prospective cohort study	604 pregnancies exposed during the 3rd trimester 1,192 pregnancies exposed only during 1st and 2nd trimester	Questionnaires	No significant association with fetal renal toxicity during the 3rd trimester	(Dathe *et al.*, 2019)

Table 9. Studies on pregnancy outcomes following *in utero* exposure to OTC analgesics

Study details						Results	
Outcome Category	**Analgesic**	**Study time**	**Study type**	**Cohort**	**Data collection method**	**Main study results**	**Study**
Pregnancy outcome							
	NSAIDs	1977-1998	Cohort and case-control study	Cohort: 1,462 women with NSAID prescription 17,259 women without prescription Case-control: 4,268 miscarriage cases 29,750 live birth controls	Prescription records, diagnosis records	Higher risk of miscarriage, no association with adverse birth outcome	(Nielsen *et al.*, 2001)
	NSAIDs, aspirin	1996-1998	Prospective cohort study	1,055 participants	Interviews, medical records checks	Higher risk of miscarriage	(Li *et al.* , 2003)
	Ibuprofen	2000-2006	Retrospective cohort study	1,117 participants	Questionnaires	No significant association with spontaneous abortion or major birth defects	(Dathe *et al.*, 2018)
	NSAIDs	2003-2009	Retrospective cohort study	65,457 participants	Medical records and databases	No significant association with spontaneous abortion	(Daniel *et al.*, 2014)
	NSAIDs	2004-2010	Prospective cohort study	2,780 participants	Medical records and interviews	No significant association with	(Edwards *et al.*, 2012)

						spontaneous abortion	
	Aspirin	Included studies up to 2001	Meta-analysis of randomised controlled studies	182 studies	Searches in Medline, Embase, Toxline, EBM Cochrane Database of Systematic Reviews and Reproductive Toxicology	No significant association with miscarriage	(Kozer *et al.*, 2003)
	NSAIDs	1997-not specified	Nested case-control study	4,705 cases of spontaneous abortion 47,050 controls	Medical records	Higher risk for spontaneous abortion	(Nakhai-Pour *et al.*, 2011)

Table 8. Studies on other perinatal offspring outcomes following *in utero* exposure to OTC analgesics

Study details						Results	
Outcome Category	**Analgesic**	**Study time**	**Study type**	**Cohort**	**Data collection method**	**Main study results**	**Study**
Other perinatal outcomes							
	Paracetamol	1976-1998	Case-control study	73 cases with amnion rupture sequence 11 cases with body wall complex 12,227 controls	Interviews, Offspring malformations were identified at birth	Higher risk for amnion rupture sequence when used during the 1st pregnancy trimester	(Werler *et al.*, 2003)
	Paracetamol	2009-2013	Prospective cohort study	2,291 participants	Interviews, Fetal growth assessed via ultrasound measurements	No association with growth of the fetus during pregnancy	(Smarr *et al.*, 2019)
	Paracetamol, aspirin	1995-1999	Case-control study	206 gastroschisis cases 126 small intestinal atresia cases 798 controls	Interviews, Offspring malformations were identified at birth	Higher risk for gastroschisis when consumed in early pregnancy	(Werler *et al.*, 2002)
	Aspirin	Included studies up to 2000	Systematic review and meta-analysis	22 studies	Searches in Medline, Embase, Toxline and EBM Reviews-Cochrane Database of Systematic Reviews,	Higher risk for gastroschisis when consumed during the 1st trimester	(Kozer *et al.*, 2002)

	Aspirin, ibuprofen	1989-1990	Case-control	110 birth defect cases 220 controls	Questionnaires, Offspring malformations identified at birth – information on clinical records	Higher risk for gastroschisis when consumed during the 1st trimester	(Torfs *et al.*, 1996)
	Diclofenac	1988-2008	Prospective cohort study	145 pregnant women exposed to diclofenac 501 controls	Questionnaires and interviews	No significant association with major birth defects following consumption during the 1st trimester	(Cassina *et al.*, 2010)
	Diclofenac	2000-2015	Prospective cohort study	260 women exposed to diclofenac 778 controls	Questionnaires and interviews	No significant association with major birth defects or spontaneous abortion following consumption during the 1st trimester	(Padberg *et al.*, 2018)
	NSAIDs	1999-2006	Prospective cohort study	69,929	Questionnaires, offspring birth defects identified in the first week after birth	No significant association with major birth defects following consumption during the 1st trimester	(van Gelder *et al.*, 2011)

	NSAIDs	1997-2001	Case-control study	29,078 birth defect cases and 10,962 controls	Interviews, pregnancy calendars, questionnaires	Higher risk for major birth defects compared to paracetamol	(Interrante *et al.*, 2017)
	Paracetamol (overdose during pregnancy)	1976-1985	Case study	60 cases	Telephone consultation and detection of paracetamol plasma concentrations	No association with birth defects, significant association of time to treatment with spontaneous abortion and fetal death	(Riggs *et al.*, 1989)
	Paracetamol (overdose during pregnancy)	1984-1992	Case study	300 cases	Questionnaires	No association with birth defects or pregnancy termination	(McElhatton *et al.*, 1997)

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

Running Title: Over-the-counter analgesia during pregnancy

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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 *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.

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.

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~~ 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.*,

2013). 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*

vitro and *in vivo* 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 trans-placental transport (Iqbal *et al.*, 2012; Walker *et al.*, 2017). They are found on both apical (syncytial microvillous) 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.*,

2013). 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).

646

647 **Other perinatal outcomes**

648 Adverse effects on the offspring at birth have also been associated with *in utero*
649 analgesics exposure (Table 8). A study by Werler and colleagues demonstrated a
650 significant association between paracetamol use during the first trimester of
651 pregnancy and the development of amniotic band defects (Werler *et al.*, 2003). In
652 another case-control study by the same group, gastroschisis was associated with
653 paracetamol and aspirin use during early pregnancy and was independent from
654 maternal symptoms (Werler *et al.*, 2002). An increased risk for gastroschisis was
655 also reported in infants after aspirin exposure during the first trimester of pregnancy
656 in a meta-analysis of the literature (Kozer *et al.*, 2002). These results were in
657 agreement with a previous study by Torfs and colleagues, associating aspirin and
658 ibuprofen (but not paracetamol) consumption during pregnancy with increased risk
659 for gastroschisis (Torfs *et al.*, 1996). Conversely, diclofenac use during the first was
660 not found to have a significant association with major birth defects (Cassina *et al.*,
661 2010; Padberg *et al.*, 2018). Similar results were also reported for use of multiple
662 NSAIDs during the first 12 weeks of gestation where no association with major birth
663 defects in the offspring was found (van Gelder *et al.*, 2011). A USA cohort study
664 comparing the incidence of birth defects between the use of NSAIDs and
665 paracetamol, showed that NSAID consumption during pregnancy can result in higher
666 risk for gastroschisis, hypospadias, cleft palate, cleft lip, anencephaly and spina
667 bifida than paracetamol in-utero exposure (Interrante *et al.*, 2017). On the other
668 hand, two studies reporting 60 and 300 cases of paracetamol overdose during
669 pregnancy, did not show strong associations with fetal toxicity or other adverse
670 outcomes (Riggs *et al.*, 1989; McElhatton *et al.*, 1997). It should be noted that these

671 women were treated for overdoses with N-acetylcysteine, ipecac or methionine.
672 Finally, no association was observed with paracetamol use and general fetal growth
673 during pregnancy in a prospective cohort study including 2,291 women (Smarr *et al.*,
674 2019).
675
676 **Pregnancy outcome**
677 Considerable effort has been focussed on pregnancy-specific outcomes following
678 OTC exposure (Table 9). A case-control study in Denmark reported an increased
679 risk of miscarriage after the use of NSAIDs during pregnancy, with the highest risk
680 when consumed 1 week before the miscarriage (Nielsen *et al.*, 2001). Two years
681 later, another cohort study in San Francisco, USA, provided similar findings, with a
682 higher risk of miscarriage reported following prenatal exposure to NSAIDs and
683 aspirin, however, not paracetamol (Li *et al.*, 2003). In contrast, a cohort study in
684 Germany did not find any significant association between ibuprofen exposure during
685 the first trimester and major birth defects in the offspring or spontaneous abortion
686 rates (Dathe *et al.*, 2018). The same results were observed in another German study
687 using the same cohort, but considering diclofenac use during pregnancy (Padberg *et*
688 *al.*, 2018). Spontaneous abortion was also not significantly associated with multiple
689 NSAID consumption either during pregnancy or periconceptional in two further
690 cohort studies (Daniel *et al.*, 2014; Edwards *et al.*, 2012). In addition, when
691 considering aspirin only, a meta-analysis of randomised controlled studies showed
692 no significant association with miscarriage rates (Kozer *et al.*, 2003). A positive
693 association was however reported by a case-control study considering multiple
694 NSAIDs and spontaneous abortion risk (Nakhai-Pour *et al.*, 2011). Finally, a
695 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

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 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

771 could be explained by sex-specific endocrine disruption and/or abnormal androgen
772 endocrinology during fetal life.
773
774 Another plausible explanation for the adverse effects of analgesics could be via their
775 association with prostaglandins. Prostaglandins are important components for
776 pregnancy and parturition as they stimulate uterine contractions and enhance
777 cervical ripening. NSAIDs inhibit cyclo-oxygenase (COX) enzymes and therefore
778 downregulate prostaglandin synthesis and prolong gestation and labour. Premature
779 labour can be successfully prevented using ibuprofen, aspirin, diclofenac and
780 ketoprofen, all available over-the-counter (Dawood, 1993; Lewis and Schulman,
781 1973). These properties could therefore explain the observed associations of their
782 use during pregnancy and miscarriage. Prostaglandins are also important regulators
783 of embryonic and fetal reproductive development as demonstrated in mice models
784 (Gupta, 1989; Gupta and Goldman, 1986). Inhibition of the prostaglandin pathway
785 during gestation can therefore also interact with human fetal reproductive system
786 development, leading to the observed neonatal reproductive outcomes. Despite their
787 well-understood functions, little information is available about COX enzyme
788 expression and role during fetal life. A rat study showed their expression in fetal skin,
789 cartilage, brain, heart and kidney (Stanfield *et al.*, 2003), while experiments using
790 transgenic mice demonstrated the importance of COX2 in normal fetal development
791 (Shim *et al.*, 2010). Reported outcomes of *in utero* exposure could therefore be due
792 to tissue-specific inhibition of COX enzymes, possibly dependant on gestation,
793 quantity and frequency of exposure.
794

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, Messerlian *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.