Development of an adverse outcome pathway for intrahepatic cholestasis of pregnancy

Jennifer Waspe a,⇑, Anna Beronius b

a Sheffield Teaching Hospitals, Glossop Road, Broomhall, Sheffield S10 2JF, United Kingdom
b Institute of Environmental Medicine, Karolinska Institutet, Sweden

ARTICLE INFO

Keywords:
Cholestasis
Adverse outcome pathway
Reproductive medicine
Pregnancy

ABSTRACT

Adverse Outcome Pathways (AOPs) are a research synthesis tool, used primarily by toxicologists for numerous applications including: hypothesis generation, data integration, biomarker determination, and identification of gaps in current knowledge. The AOP model provides a means for evaluating critical interactions between stressors and biological systems which result in adversity, meaning there is significant potential value in using this model in clinical research. However, AOPs have so far not been applied in this context, which may be attributable to the fact that the method is not yet streamlined with established practices in evidence-based medicine, such as systematic review.

Here, we present one approach to developing a clinically focused AOP for intrahepatic cholestasis of pregnancy; aiming to enhance understanding of the mechanistic link between this common, gestational liver disease and its association with preterm birth.

Mechanistic aspects of the disease pathogenesis, and use of AOPs to broaden inclusion and improve integration of in vitro and in vivo data in clinical research are discussed.

We also demonstrate for the first time how central components of systematic review can be integrated into the development of an AOP.

Introduction

Intrahepatic cholestasis of pregnancy (ICP) is a complex disease of abnormal bile acid metabolism associated with adverse perinatal outcomes; in particular, spontaneous preterm birth is reported in up to 44% of affected women (Floreani and Gervasi, 2016; Diken et al., 2014; Alsulyman et al., 1996). The cause of this condition is unknown; however, genetic, environmental and infectious aetiologies have all been implicated (Diken et al., 2014). Currently, there are limited biomarkers for disease severity or risk stratification, so it is difficult to monitor affected mothers, or determine the optimal timing of delivery (Arthuis et al., 2020).

Cholestasis is frequently encountered as a toxic endpoint in chemical risk assessment (Noor, 2015) and consequently bile acid metabolism has been studied extensively by toxicologists. One approach to understanding complex problems in toxicology is the development of Adverse Outcome Pathways (AOPs). The AOP framework is endorsed by the Organisation for Economic Co-operation and Development (OECD) and other international regulatory bodies to concisely review the evidence causally linking indicators of molecular, cellular, tissue and organ level dysfunction to adverse health effects (Villeneuve et al., 2014). An AOP starts with a ‘Molecular Initiating Event’- MIE, and ends with an ‘Adverse Outcome’- AO (Fig. 1a). The MIE and AO are connected via measurable and essential ‘Key Events’ (KE). Each KE is supported by a KE description which summarises the current biological understanding, methods for measuring the KE and the species exhibiting the KE (the biological domain of applicability). Adjacent KEs in an AOP are linked by ‘Key Event Relationships’ (KER) supported by KER descriptions. These constitute summaries of the biological plausibility, empirical evidence and consistency of experimental outcomes supporting the KER. There is detailed methodological guidance for developing AOPs, including a structured evaluation process (Villeneuve et al., 2014; OECD, 2018).

Despite the rigorous approach to evidence synthesis at the core of AOP development, systematic review principles are not integral to the framework. This might raise concerns among clinicians about the reliability of AOPs (Wood et al., 2008). At present, implementation of systematic review principles more broadly in toxicology is desirable.
but contentious (Whaley et al., 2016). There are pragmatic difficulties designing a search strategy and approach to study evaluation that can accommodate the spectrum of subject areas and study types characteristic of an AOP, inclusive of molecular through to population level events. Nevertheless, to achieve wider, interdisciplinary acceptance of the AOP framework, these aspects are likely to be required.

Here, we use the AOP framework to examine one aspect of ICP pathogenesis: inhibition of the nuclear receptor Farnesoid X receptor (FXR) leading to spontaneous preterm birth. This AOP does not examine sudden fetal demise, which is also a clinical concern in women with ICP. We demonstrate multilevel evidence synthesis in a clinical context, indicate current gaps in ICP research and for the first time, demonstrate one approach to integrating AOP development and systematic review.

Materials and methods

The method for AOP development used here was based on the OECD Users’ Handbook supplement to the Guidance Document for developing and assessing AOPs (OECD, 2018). In addition, a systematic approach to evidence evaluation was adapted from the Handbook for Conducting a Literature-Based Health Assessment using the Office of Health Assessment and Translation Approach for Systematic Review and Evidence Integration (OHAT, 2015) and the Science in Risk Assessment and Policy tool (SciRAP) (Molander et al., 2015; Roth et al., 2021). Briefly, structured searches inclusive of Web of Science, Embase, PubMed, the Cochrane Library and Medline (Ovid), including in-process and other non-indexed citations, were undertaken on 8th December 2016 and 1st February 2017, respectively. The search strategy combined the following keyword and MeSH terms—including all subheadings: “obstetric,” “pregnancy,” “cholestasis” and “intrahepatic cholestasis,” combined using Boolean operators OR/AND, and was approved in advance by information specialists at the Karolinska Institute Library. ‘Obstetric cholestasis’ (OC) is synonymous to the term ‘intrahepatic cholestasis of pregnancy’ and the search was designed to identify articles where the diagnostic criteria for this condition had been carefully considered. Duplicate articles were removed and results were limited to journal articles and reviews published after 1st January 2003. This date restriction was chosen to match that set during development of the 2011 Royal College of Obstetrics and Gynecology (UK) guidance document on the diagnosis and management of ICP (RCOG, 2011).

Titles and abstracts of articles identified in the search were screened by a single reviewer against pre-defined exclusion criteria (Fig. 2); only articles specifying OC or ICP were included. Relevant articles were imported to an Endnote library and stratified by publication type. Review articles were read in full by a single reviewer and used to map out the scope of current understanding of ICP.

Journal article titles and abstracts were screened by the same reviewer and stratified by main focus or outcome measure. Well studied areas were identified as possible KEs. These were arranged into a putative AOP network, beginning with KEs at the lowest level of biological organization i.e. molecular, and moving up to an individual or population level. The resulting network was compared to the results of the scoping exercise and any major discrepancies identified.

One AOP from the network was evaluated in full. Each constituent KE was developed into a KE description, encompassing research on current biological understanding, methods for quantification and the biological domain of applicability i.e. the species, sex and life stage of subjects relevant to the KE. As an example, the biological domain of applicability for ‘KE: increased oxytocin receptor expression during labour’ would be restricted to female mammals with reproductive potential.

The empirical evidence for developing each KE into a KER description was assembled as follows. A single reviewer re-screened the titles and abstracts of journal articles in the Endnote library, and collated relevant studies or study endpoints according to pre-defined exclusion criteria for each KER (Fig. 2). The reference lists of these articles were searched for additional records. Data was extracted and entered into evidence tables with pre-defined headings. For in vitro and in vivo studies: an article’s rationale, details of any stressor (i.e. application of a chemical or other exposure prompting one KE to lead to the next KE), the species tested, the dose range used, the duration of
exposure, observed effects, and whether dose–response effects were seen, were recorded. For studies involving human subjects: an article identifier, population studied, effects observed and statistical data were tabulated. If no empirical evidence was identified from the Endnote library a separate literature search was undertaken to encompass experiments undertaken in different contexts. Details of secondary literature searches were recorded separately.

All included studies underwent a reliability assessment using the SciRAP tool (Molander et al., 2015) or a variant thereof. We acknowledge that SciRAP is not a validated tool for evidence appraisal in this setting, therefore this exercise was to explore possible avenues for evidence appraisal during future AOP development. No studies were excluded on this basis, and the outcomes are not discussed in this text.

Evidence for the biological plausibility of each KER was compiled by the authors and inconsistencies in empirical evidence were considered and recorded separately.

To standardize the evaluation of AOPs, the OECD handbook (OECD, 2018) provides guiding questions for grading four major and one optional aspect of the AOP. The combined results of these give a confidence rating for the AOP as a whole. In this case, four major aspects were evaluated:

- The biological domain of applicability of the whole AOP
- The essentiality of each KE i.e. the extent to which each KE is essential for progression to the subsequent KE
- The biological plausibility of each KER
- The biological plausibility of each KER
- The empirical evidence for each KER

No statistical analysis was performed as this is not part of the AOP development process. Ethical permission was not required for this analysis of pre-published literature.

Results

Results of the literature search

Results of the literature search are shown as a PRISMA-style diagram (Fig. 2) (Moher et al., 2009). Briefly, 445 articles were screened by title and abstract. Of these, 35 review articles were used to define the current scope of ICP research. Screening of the remaining 410 journal abstracts identified possible KEs and facilitated building a putative AOP network (Fig. 3). No discrepancies between this network and the scoping exercise were identified.

Summary results of the AOP

The proposed AOP: inhibition of FXR leading to increased prevalence of spontaneous preterm birth is presented in Fig. 1b. This AOP comprises 5 KEs and four KERs. This AOP was selected for evaluation due to the clear sequence of KEs at each level of biological organization. This is a preferred situation in AOP development, as it creates a basis for predicting outcomes at higher levels (i.e. in a tissue or organism), using measurements taken at lower levels (i.e. cellular or molecular level) (OECD, 2018).

Evaluation of the AOP: Biological domain of applicability

KEs 1–3 represent biological processes which are essential to human health as well as mammals and fish of both sexes and at all life stages (Koutsounas et al., 2015; Gadaleta et al., 2010). KE 4 is restricted in applicability to mammals, since the presence of a uterus is essential for its contractility to be affected by any process. Preterm birth in mammals other than humans is little researched and there is little intervention when it occurs, as such, the relevance of spontaneous preterm birth is almost exclusive to humans (Phillips et al., 2015). In this study, the domain of applicability is limited to human females.

Evaluation of the AOP: Essentiality of KEs

All KEs in this AOP were graded as having high essentiality, meaning there was direct evidence that blocking an earlier KE prevented one or more later KEs (see Fig. 1c):

- KE1: Substantial experimental evidence demonstrates that antagonizing or silencing FXR inhibits transcription of genes involved in bile acid metabolism (Li et al., 2016; Li et al., 2016; Chen et al., 2015; Song et al., 2014; Abu-Hayyeh et al., 2013; Lien et al., 2014), and can raise bile acids (Li et al., 2016; Li et al., 2016; Lien et al., 2014). FXR agonists increase transcription of these genes (Li et al., 2016; Song et al., 2014; Abu-Hayyeh et al., 2013; Lien et al., 2014; Plass et al., 2002; Milona et al., 2010).
- KE2: Well-characterized FXR target genes cause elevation in bile acids if inhibited at mRNA or protein level (Li et al., 2016; Li et al., 2016; Lien et al., 2014; Trauner et al., 1997; Vallejo et al., 2006; Liu et al., 2003; Barth et al., 2003).
- KE3: Direct in vitro and epidemiological evidence that elevated bile acids result in a higher frequency of uterine contractions compared to controls (Israel et al., 1986; Germain et al., 2003; Zhao et al., 2014), plus some in vivo evidence that exposure to bile acids results in spontaneous preterm birth (Campos et al., 1986; Perez et al., 1994).
- KE4: Supporting in vitro and human data that the uterotonin stimulates more frequent contractions if the biochemical environment contains higher bile acids (Israel et al., 1986; Germain et al., 2003). In addition, threatened pre-term labor is managed with agents to relax the uterus and suppress contractions (Tsatsaris et al., 2004).

**Evaluation of the AOP: Biological plausibility of KERs**

Biological plausibility is based on whether there is a demonstrable mechanistic link between two KERs, in keeping with known biological relationships (OECD, 2018). Guidance for grading biological plausibility incorporates modified Bradford Hill criteria (OECD, 2018), and is used to address the defining question: is there an established mechanistic relationship between the two KERs constituting the KER (OECD, 2018). Briefly, for a KER where there is broad acceptance of the proposed relationship and supporting mechanistic evidence, biological plausibility is considered high; for a KER where there is support according to analogy to other biological phenomena but incomplete understanding of the relationship in question, biological plausibility is considered moderate. In cases where there is statistical demonstration but poor biological understanding, the biological plausibility of the KER is graded as low (OECD, 2018). In this AOP the biological plausibility of KER1 was graded as moderate; although the exact mechanistic basis of FXR function is unclear, there is broad acceptance that activation of FXR in response to ligand binding and removal of co-repressors is required for target gene transcription, and inhibition of this process prevents downstream effects (Tu et al., 2000; Gronemeyer et al., 2004). KER2 was graded as high, owing to the well-established relationship between bile acid transporters and serum bile acid levels (Chiang, 2013). KER3 was graded as moderate; although specific understanding of the control of uterine contractions has not been established, there is available evidence to support several proposed pathways through which increased levels of bile acids in pregnancy may augment underlying biological regulation of uterine activity (Germain et al., 2003; Ahanya et al., 2005; Šimják et al., 2015). One such example includes increased myometrial oxytocin receptor expression in women with ICP, (Germain et al., 2003) which is particularly significant given the established importance of oxytocin in the initiation and progression of labour at any gestation (Laudanski and Pierzynski, 2003; Uvnäs-Moberg et al., 2019). However, the inability of oxytocin receptor antagonists to reliably arrest preterm labour in women without ICP indicates specific mechanistic control of labour in circumstances including pre-term birth is inadequately understood to grade this KER as high. Finally, KER4 was graded as low; uterine contractions are one of several processes considered essential for parturition, however at present there is insufficient biological understanding of these processes and the factors controlling their initiation to conclude on the regulation of human birth and its timing i.e. term vs pre-term (Gimpl and Fahrenholz, 2001).

**Evaluation of the AOP: Empirical evidence for KERs**

Overall, 40 endpoints from 18 studies were found to be relevant to KER1; 26 endpoints from 18 studies relevant to KER2 and 9 endpoints from 5 studies relevant to KER3. For KER4 a new literature search was undertaken as this relationship was too poorly represented by the data in the original literature search. From this, 12 endpoints from 12 studies were found to be relevant to KER4. Details of the search and exclusion criteria for all KERs are shown in Fig. 2.

Empirical support carries less overall influence in concluding on confidence in an AOP compared to assessments of essentiality or biological plausibility (OECD, 2018) and can also be graded as high (a change in a downstream KER is demonstrated in response to multiple specific stressors), moderate (the relationship is demonstrated by few stressors, or inconsistencies are found in available data) or low (limited information is available or inconsistencies are significant). The empirical support for KERs in this AOP was rated as high for KERs 1 and 2 and moderate for KERs 3 and 4 (Fig. 1d).

**Evaluation of the AOP: Overall confidence**

Taking together the results of the domain of applicability, essentiality of KEs, biological plausibility and empirical support of KERs, the overall confidence in this AOP was concluded as moderate to high. KERs 3 and 4 were both graded as having moderate empirical support, and moderate or low biological plausibility respectively. This reduced confidence in the AOP overall and was primarily attributable to aspects of parturition which are poorly characterized.

**Discussion**

In this paper we describe the process of developing an AOP network (Fig. 3) for ICP and evaluation of one AOP therein. In addition, we demonstrate one method for incorporating systematic review principles in the identification of relevant literature for the AOP network and for individual KERs. Based on recommended evaluation methods (OECD, 2018) confidence in this AOP was deemed moderate to high.

There are a number of methodological limitations to this work, which will be discussed in turn. Firstly, supporting evidence for this AOP was not collected after February 2017. Although this means the evidence base for the AOP is outdated, the decision was made not to retrospectively add data from newer studies. Instead, we intend to repeat the AOP process as a structured update and demonstrate how evidence for KEs and KERs can gradually be strengthened with multiple iterations, evolving in line with increasing evidence. It would be particularly advantageous if newer studies were found to address research gaps in the AOP or result in modifications to the proposed pathway. Secondly, although current guidance on AOP development does not require a risk-of-bias evaluation to be undertaken, we acknowledge that this is absent in this work. Here, the SciRAP tool was used as an example of a systematic approach to evidence appraisal which could be included in the evidence evaluation process; particularly to improve the robustness and transparency of AOP evaluations. The SciRAP tool has been developed for the purpose of evaluation of toxicity studies and provides criteria to evaluate aspects of reliability, in contrast to risk-of-bias domains as traditionally done in systematic review (Waspe et al., 2021). Importantly, studies were not excluded from analysis based on the SciRAP evaluation. The scope of a reliability assessment cannot be considered directly equivalent to a risk-of-bias evaluation (Waspe et al., 2021) and targeted approaches to consistent evaluation across different study types are required. It is hoped that further work will result in a concrete proposal for incorporating critical appraisal into the AOP framework. Finally, it is usual practice for two or more reviewers to consider inclusion and exclusion of studies in a systematic review and for discrepancies to be discussed by a third, external reviewer (OSHAT, 2015). Resource limitations meant this was not possible, however retrospective re-evaluation could be undertaken as all decisions have been clearly documented throughout and search results archived. This may have a downstream effect on the
results of the AOP, which can be accommodated by the framework of AOPs as ‘living documents’ (OECD, 2018).

The utility of AOPs in a clinical context should also be discussed. An AOP is a clear and reproducible way of summarizing the distribution of evidence contained in large numbers of studies in one infographic; the AOP shown here incorporates endpoints from more than 60 research articles, which exceeds the number usually encompassed in a single systematic review. Rapid access to the evidence base for specific biological relationships as well as distinct pathologies has many advantages, particularly when mechanistic aspects and epidemiological associations are encompassed. In turn this information can be used for hypothesis generation, to expose areas of poor understanding and to identify potential biomarkers for focusing future research. However, AOPs do not necessarily provide answers and do not take the place of primary research, systematic review or meta-analysis, instead being considered an adjunct to these methods.

The least well supported aspects of the AOP presented here relate to the poorly understood nature of labor initiation and the characterization of uterine contractions throughout gestation (Kota et al., 2013; Vinken et al., 2009). It is impressive that a small number of experiments have been conducted to support the influence of bile acids on uterine contractility, however, these data are limited, and these limitations are seen in the AOP. Furthermore, the biochemical control of parturition is highly sophisticated, incorporating complex signaling cascades between the fetus and fetal membranes, as well as maternal reproductive tract. This AOP does not explore the impact of altered bile acid metabolism on such tissues. However, emerging technologies such as Fetal-Membrane-Organ-on-Chip devices, may well facilitate examination of this delicate hormonal interplay (Richardson et al., 2020).

AOPs describe the consequences to a biological system once sufficient stress causes homeostatic mechanisms to be exceeded. Therefore, given the vast adaptive capacity of living organisms to cope with bile acid stress, this work supports the idea that at the point of diagnosing ICP, metabolic disruption is already severe. Given the high incidence of gestational diabetes among suffers of ICP this aspect may also warrant further attention (Martineau et al., 2014).

ICP is an uncomfortable and anxiety provoking condition for sufferers and their families, and there is great need to improve identification of those at highest risk of fetal compromise (Geenes and Williamson, 2009; Walker et al., 2002). Ideally, systematic integration of mechanistic and epidemiological data would provide much needed insight into this and other poorly understood conditions; adoption of the AOP framework may well be key in achieving this.

Data availability

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

CRediT authorship contribution statement

Jennifer Waspe: Conceptualization, Methodology, Investigation, Writing – original draft. Anna Beronius: Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Many thanks to Professor Hanns-Ulrich Marschall for his support in developing this work.

References

Abu-Hayyeh, S., Papacalouzou, G., Lövgren-Sandblom, A., Tahir, M., Odwowe, O., Jamaludin, N.A., Ravat, S., Nikolova, V., Chambers, J., Selden, C., Rees, M., Marschall, H.-U., Parker, M.G., Williamson, C., 2013. Intrahepatic cholestasis of pregnancy levels of sulfated progesterone metabolites inhibit farnesoid X receptor resulting in a cholestatic phenotype. Hepatology 57 (2), 716–726.

Ahanya, S.N., Lakshmanan, J., Morgan, B.L.G., Ross, M.G., 2005. Meconium passage in uterine mechanisms, consequences and management. Obstet. Gynecol. Surv. 60 (1), 45–56.

Altsuler, O.M., Ououzian, J.G., Ames-Castro, M., et al, 1996. Intrahepatic cholestasis of pregnancy: perinatal outcome associated with expectant management. Am. J. Obstet. Gynecol. 175 (4), 957–960.

Arthuis, C., Diguisto, C., Lorphelin, H., Doctor, V., Simon, E., Perrotin, F., Winer, N., Alpini, G.D., 2020. Perinatal outcomes of intrahepatic cholestasis during pregnancy: a meta-analysis of case-control studies. Plast Reconstr Surg 135 (2), e6021–e6025.

Barth, A., Klinger, G., Rost, M., 2003. Influence of ethylenglycol propanolsulfonate on serum bile acids in healthy volunteers. Exp. Toxicol. Pathol. 54 (5–6), 381–386.

Campos, G.A., Guerra, F.A., Ireland, E.J., 1986. Effects of cholic acid infusion in fetal lambs. Acta Obstet. Gynecol. Scand. 65 (1), 23–26.

Chen, Y., Vasilenko, A., Song, X., et al, 2015. Estrogen and Estrogen Receptor alpha Mediated Transrepression of Bile Salt Export Pump Molecular Endocrinology. 29 (4):613–626.

Chiang, Y.J.L., 2013. Bile acid metabolism and signaling. Comprehensive Physiol. 3 (3), 1191–1212.

Diken, Z., Utsa, I.M., Nassar, A.H., 2014. Clinical approach to intrahepatic cholestasis of pregnancy. Am. J. Perinatol. 31, 1–8.

Florani, A., Gervasi, M.T., 2016. New insights on intrahepatic cholestasis of pregnancy. Clin. Liver Dis. 20 (1), 177–189.

Gadaleta, R.M., van Mil, S.W.C., Oldenburg, B., Siersema, P.D., Klomp, L.W.J., van Erpecum, K.J., 2010. Bile acids and their nuclear receptor FXR: relevance for hepatobiliary and gastrointestinal disease. BBA 1801 (7), 683–692.

Geenes, V., Williamson, C., 2009. Intrahepatic cholestasis of pregnancy. World J. Gastroenterol. 15 (17), 2049–2066.

Germain, A.M., Kato, S., Carvajal, J.A., Valenzuela, G.J., Valdes, G.L., Glinisnoc, J.C., 2003. Bile acids increase response and expression of human myometrial oxytocin receptor. Am. J. Obstet. Gynecol. 189 (2), 577–582.

Gimpl, G., Fahrenholz, F., 2001. The oxytocin receptor system: structure, function, and regulation. Physiol. Rev. 81 (2), 629–662.

Gronemeyer, H., Gustafsson, J.-Å., Laudet, V., 2004. Principles for modulation of the nuclear receptor superfamily. Nat. Rev. Drug Discovery 3 (11), 950–964.

Israel, E.J., Guzman, M.L., Campos, G.A., 1986. Maximal response to oxytocin of the fetoplacental circulation in the sheep. Am. J. Obstet. Gynecol. 155 (4), 613–626.

Koutsounas, I., Theocharis, S., Delladetsima, I., Patsouris, E., Giaginis, C., 2015. Farnesoid X receptor function. Hepatology 52 (4), 1341–1349.

Kotliar, J., Olaussen, K.A., Gjaltema, J.A., Auriol, D., Desideri, G., Van Loo, P., 2013. Farnesoid X receptor agonist GW4064 in rat models of intra- and extrahepatic cholestasis. J. Clin. Investig. 124 (3), 1037–1051.

Kuo, Y., Li, C., Liu, L., Li, C., Wang, Y., Zhang, Y., 2017. Clinical evidence of elevated bile acids and decreased farnesoid X receptor expression in liver diseases. J. Physiol. 593 (23), 5043–5055.

Kuo, Y., Li, C., Liu, L., Li, C., Wang, Y., Zhang, Y., 2017. Clinical evidence of elevated bile acids and decreased farnesoid X receptor expression in liver diseases. J. Physiol. 593 (23), 5043–5055.
Of Perez, R., Garcia, M., Ulloa, N., Jara, C., Bardisa, L., Rudolph, M.I., 1994. A single Tsatsaris, V., Cabrol, D., Carbonne, B., 2004. Pharmacokinetics of Tocolytic Agents. Clin. Pharmacol. 43 (13), 833–844.

Tu, H., Okamoto, A.Y., Shan, B., 2000. FXR, a bile acid receptor and biological sensor. Trends Cardiovasc. Med. 10 (1), 30–35.

Uvnás-Moberg, K., Ekström-Bergström, A., Berg, M., Buckley, S., Pajzic, Z., Hadjigeorgiou, E., Kottowska, A., Lengler, L., Kielbasańska, B., Leon-Lario, F., Magistretti, C.M., Downe, S., Lindström, B., Dencker, A., 2019. Maternal plasma levels of oxytocin during physiological childbirth – a systematic review with implications for uterine contractions and central actions of oxytocin. BMC Pregnancy Childbirth. 19 (1), 285.

Vallejo, M., Briz, O., Serrano, M.A., Monte, M.J., Marin, J.J.G., 2006. Potential role of trans-inhibition of the bile salt export pump by progesterone metabolites in the etiopathogenesis of intrahepatic cholestasis of pregnancy. J. Hepatol. 44 (6), 1150–1157.

Villeneuve, D.L., Crump, D., Garcia-Reyero, N., Hecker, M., Hutchinson, T.H., Lalonde, C. A., Landesmann, B., Lentiari, T., Munn, S., Nepelska, M., Ortinger, M.A., Vergauwen, L., Whelan, M., 2014. Adverse Outcome Pathway (AOP) development I: strategies and principles. Toxicol. Sci. 142 (2), 312–320.

Vinken, M.P.G.C., Rabotti, C., Michi, M., Oei, S.G., 2009. Accuracy of frequency-related parameters of the elektrohysterogram for predicting preterm delivery: a review of the literature. Obstet. Gynecol. Surv. 64 (8), 529–541.

Walker, I.A.L., Nelson-Piercy, C., Williamson, C., 2002. Role of bile acid measurement in pregnancy. Ann. Clin. Biochem. 39 (2), 105–113.

Waspe, J., Bui, T., Dishaw, L., Kraft, A., Luke, A., Beronius, A., 2021. Evaluating reliability and risk of bias of in vivo animal data for risk assessment of chemicals – exploring the use of the SciRAP tool in a systematic review context. Environ. Int. 146, 106103.

Whaley, P., Haball, C., Gerstrand, M., Aiassa, E., Benford, D., Bilotta, G., Coggon, D., Collins, C., Dempsey, C., Duarte-Davidson, R., FirzGerald, R., Galay-Burgos, M., Gee, D., Hoffmann, S., Lam, J., Lasserson, T., Levy, L., Lipworth, S., Ross, S.M., Martin, O., Meads, C., Meyer-Baron, M., Miller, J., Pease, C., Rooney, A., Sapie, D., Stewart, G., Taylor, D., 2016. Implementing systematic review techniques in chemical risk assessment: challenges, opportunities and recommendations. Environ. Int. 92-93, 556-564.

Wood, L., Egger, M., Gruud, L.L., Schulz, K.F., Juni, P., Altman, D.G., Gruud, C., Martin, R.M., Wood, A.J.G., Sterne, J.A.C., 2008. Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. BMJ 336 (7444), 601–605.

Zhao, P., Zhang, K., Yao, Q., Yang, X., 2014. Uterine contractility in intrahepatic cholestasis of pregnancy. J. Obstet. Gynaecol. 34 (3), 221–224.