

## Risk perception regarding drug use in pregnancy



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Only about 1% of all birth defects are caused by maternal drug use. However, it has been shown that pregnant women perceive teratogenic risks of drug use to be unrealistically high.<sup>1-4</sup> The erroneous perception of teratogenic risk is often shared by health care professionals.<sup>2,5-8</sup> In this Clinical Opinion, we will focus on possible explanations and consequences related to this issue. We will also present some suggestions for risk communication that could result in a more rational clinical practice.

Our perspective is 20 years' experience of a Norwegian network of drug information centers (RELIS), in which questions about drug use in pregnancy represent about 13% of nearly 40,000 queries from health care professionals. A majority of these questions come from physicians, including both general practitioners and specialists.<sup>9</sup>

Questions to RELIS regarding pregnancy are usually patient related and decision support is requested. Such support is provided by pharmacists and clinical pharmacologists with expertise in searching and critically evaluating the literature. Since 2011, RELIS has also provided a service for pregnant or breast-feeding women (Safe Mommy

Pregnant women, but also physicians, have unrealistically high perceptions of teratogenic drug effects. This may result in suboptimal treatment of disease and even influence decisions of whether to continue pregnancy. To attain more realistic teratogenic risk perceptions, several factors that influence this issue should be considered, and these are further discussed in this Clinical Opinion. Importantly, drug use may have several benefits, both for the pregnant woman's health and to avoid negative fetal effects of untreated maternal disease. A greater focus on this aspect may act to balance risk perceptions. Furthermore, both pregnant women and physicians need access to drug information sources that provide realistic risk estimates to increase confidence in appropriate drug use and prescribing. We suggest that access to decision support and individually tailored information provided by drug information centers may contribute to this goal.

**Key words:** drug information centers, drug labeling, drug use, pregnancy, risk assessment, risk perception, teratogenic risk

Medicine), in which now more than 10,000 drug-related questions have been answered.<sup>10</sup> In this setting, pregnant women may, for example, ask for explanations of statements that they have read in various drug information sources or in the media.

### Pregnant women's risk perception

In pregnancy, managing risks become complex because the pregnant woman is responsible for the well-being of both herself and her unborn child. Most mothers put the needs of their baby first. Western societies' great focus on risks may contribute to pregnant women's overestimation of the potential danger attributed to the use of medicines.<sup>11</sup> It may be speculated that because pregnant women usually are recommended to refrain from a range of potentially dangerous activities, such as eating unpasteurized cheese or painting walls, they may believe they should at least refrain from the use of any kind of foreign substances, such as drugs.

The 1960s' discovery of birth defects caused by the use of thalidomide in early pregnancy may also still contribute to increased teratogenic risk perceptions.<sup>1</sup> Furthermore, because the media usually stress the risks related to the use of medicines rather than the benefits, this

may influence attitudes to medicine use in pregnancy.

Another aspect is that pregnant women's risk perceptions and health decisions may be influenced by the experiences, opinions, and beliefs of family and friends.<sup>12</sup> Perception of teratogenic risk has also been shown to vary with age, level of education, parity, and geographical region.<sup>13</sup>

People often overstate risks that have low probability but are dramatic, such as being in a plane crash or having a malformed child. In contrast, they tend to underestimate more common risks, for example, developing diabetes or hypertension.<sup>14</sup> This phenomenon of probability neglect may therefore contribute to the overestimation of drug-related teratogenic effects.

Drug labeling may also influence pregnant women's risk perception. Patient information leaflets, and other information provided by the pharmaceutical industry, often provide restrictive or unclear advice regarding drug use in pregnancy.<sup>15</sup> For example, the international patient information text regarding use of the antidepressant escitalopram (Ciprallex) in pregnancy is extensive and presents several details regarding possible effects on newborns after exposure in the last trimester.<sup>16</sup>

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Such detailed information may act to increase women's concerns for drug use,<sup>2</sup> and when the information in addition lacks a focus on the benefits of drug use in depression, unrealistic teratogenic risk perception may easily be the result.

Risk perceptions are determinants for confidence in the use of medicines,<sup>2,17</sup> and risk perceptions may therefore influence health behaviour. Overestimating teratogenic risks can have an impact on a woman's decision on whether to continue a pregnancy after taking a drug and whether to take prescribed medicines.<sup>12</sup> It may also induce unnecessary anxiety for using a treatment that may improve health during pregnancy.

### Physicians' risk perception

Drugs are not tested systematically in pregnant women because of the ethical issues of including expectant mothers in clinical trials. Nevertheless, physicians need to weigh risks and benefits of drug prescribing to pregnant patients, based on the available knowledge. The fact that there is scientific uncertainty regarding teratogenic risks of drug use in pregnancy may, however, increase the physician's own perception of risk.<sup>11</sup> For example, inconsistent findings about the safety of antidepressants during pregnancy may be a challenge to the physician in choices of drug prescribing.<sup>18</sup> More research on the risk of drug use in pregnancy is warranted to decrease the uncertainties related to the possible teratogenic effects of the drugs.

Product monographs often represent a first-line source for physicians who counsel pregnant women.<sup>5,19</sup> However, such information is based on disclaimers and is not applicable as a guide to decision support concerning drug use in pregnancy. In addition, product-specific information is often categorical (ie, drugs are classified according to risk evaluation based on animal studies or clinical case reports). The restrictiveness of product-specific information may itself result in increased perception of teratogenic risk among physicians. Conflicting information between product-specific information and sources that give a realistic assessment of

drug safety in pregnancy can contribute further to this issue.<sup>5</sup>

Probability neglect, as previously described, may also influence risk perception among physicians. Although lay people and experts often define risks differently, the difference decreases as experts are forced to go beyond the limits of available data and rely on intuition and extrapolation.<sup>20</sup> Therapeutic decisions in this context may also be influenced by the patient-physician relationship. For example, a woman with 2 previous spontaneous abortions would be expected to be skeptical of any drug therapy in her new pregnancy, and by communicating this to her physician, she may influence the physician's risk perception.

A consequence of physicians' erroneous risk perceptions may be that pregnant women with chronic diseases or acute pregnancy-related symptoms do not get access to necessary drug treatment.<sup>7</sup> Risk communication provided by the physician may also have a significant impact on the risk perception of the pregnant woman, and after receiving information about a possible teratogenic potential of a drug, it may be difficult for the woman to accept reassuring evidence-based drug information.<sup>8</sup>

### Toward realistic risk perception

Drug information regarding pregnancy inherently conveys teratogenic risks. Consequently, if this information is presented in such a way that realistic risks are perceived, it may result in appropriate choices regarding drug use in pregnancy.<sup>13</sup>

Several aspects are important to address in approaching realistic teratogenic risk perceptions. For pregnant women, health literacy, beliefs about medicines, empowerment, and confidence in health care systems are some examples. For physicians, the level of evidence in drug information and choice of information source are elements to consider. It would be desirable to measure the outcomes of the different interventions that may influence teratogenic risk perceptions. However, we have not been able to identify any

sources in the literature that present such outcome measurements numerically.

The concept of health literacy includes the capacity to obtain, process, and understand health information to make appropriate health decisions.<sup>21</sup> Low health literacy among pregnant women has been shown to be associated with elevated risk perception for medications<sup>22</sup> and negative beliefs about medicines.<sup>21</sup> The fact that the capacity to understand drug information influences risk perception further illustrates the need of formulating drug information in a way that is understood at all levels of health literacy.

Identical information texts may be interpreted differently by individuals because of different beliefs about medicines, level of health literacy, and situational risk assessment.<sup>23</sup> In this context, use of more or less reassuring words and terms can influence risk perceptions and confidence in the use of medicines.<sup>2,24</sup>

Negatively framed risk information (1–3% risk of having a child with malformation) may result in significantly higher risk perceptions among pregnant women compared with positively framed information (97–99% chance of having a normal child).<sup>25</sup> Information in numeric (1:1000) formats should in general be preferred to verbal formats ("rare") because both patients and health care providers may have a different understanding of the meaning of verbal descriptors. Visual aids (ie, Cates plot) may be used to depict the number of cases that may either benefit from or be harmed by a treatment.<sup>26</sup> Such aids may also be useful for communication of teratogenic risks because the baseline risk may be shown in correlation to the drug-related risk.

Understanding pregnant women's risk perception is important to achieve good risk communication strategies that empower pregnant women to have confidence in the necessary use of medicines. To counteract the overestimation of risks, a greater focus on the positive health consequences of treating medical conditions during pregnancy, both for the mother and child, should be pursued. In particular, this concerns the benefits of the use of antidepressants and

other psychotropic medicines to avoid negative outcomes for mother and child because of untreated maternal disease. Untreated depression during pregnancy may result in premature delivery, low birthweight, decreased breast-feeding initiation, and impaired mother-child bonding. It has been shown that pregnant women have low adherence to the use of psychotropic medicines but that belief in the benefits of such drug use results in increased medication adherence.<sup>18</sup>

Risk counseling may decrease high teratogenic risk perceptions among pregnant women.<sup>4</sup> Tailoring drug information according to the needs, beliefs, and perceptions of each woman could therefore increase the patient's empowerment and adherence to drug therapy.

To counsel pregnant patients according to their individual needs, physicians need access to reliable drug information with a high level of evidence. Product-specific information has no place in this context. Electronic prescription tools providing expert-evaluated information regarding risks of drug use in pregnancy may, however, be utilized.

Another suggestion is a further focus on patient-specific information provided by drug information centers and teratogen information services because such services have been found to influence both therapeutic decisions in general<sup>27,28</sup> and regarding pregnancy.<sup>9,29</sup>

The Norwegian RELIS database is a question-answer pair database containing anonymized queries from health care professionals. The RELIS database is freely accessible through a web site ([www.relis.no](http://www.relis.no)). Health care professionals who understand Scandinavian languages can utilize the database, and some Swedish drug information centers have recently joined the database. We do not have complete overview of the accessibility of question-answer pair databases provided by drug information centers internationally. However, we believe that such databases may be important as producer-independent drug information sources, for example, regarding pregnancy, for health care professionals worldwide.

In June 2015, the US Food and Drug Administration implemented the Pregnancy Lactation Labeling Rule (PPLR). The pregnancy letter categories previously included in drug labels will now be replaced by the PPLR. The PPLR has a narrative structure that provides detailed information, divided in the following subsections: risk summary, clinical considerations, data and pregnancy registry (if applicable). The introduction of the PPLR implies a greater focus on explaining the risks and benefits of drug use for the mother, fetus, and breast-feeding child.<sup>30</sup> This is an important step toward achieving our suggested goals of more realistic risk perceptions related to drug use in pregnancy.

### Conclusions and implications

Risk perception regarding drug use in pregnancy is a clinical challenge and influences rational drug therapy. Unrealistic risk perception among pregnant women and physicians are due to individual, cultural, and social factors. The scientific uncertainty regarding the risks of the teratogenic effects of drugs significantly influences the quality of the drug information. To focus on the benefits of drug use for conditions that may have negative pregnancy outcomes when untreated is essential to enable well-founded decisions regarding the use of medicines.

Our perspective is to enhance risk management through some suggestions for risk communication. For the pregnant woman, this includes empowerment and confidence in drug use. For physicians, this includes awareness of specific drug information sources that provide realistic descriptions of risk, beyond product monographs. We believe that availability of question-answer services, which provide decision support, may contribute to improved teratogenic risk management. ■

### REFERENCES

1. Nordeng H, Ystrom E, Einarson A. Perception of risk regarding the use of medications and other exposures during pregnancy. *Eur J Clin Pharmacol* 2009;66:207-14.
2. Widnes SF, Schjott J, Eide GE, Granas AG. Teratogenic risk perception and confidence in

use of medicines in pairs of pregnant women and general practitioners based on patient information leaflets. *Drug Saf* 2013;36:481-9.

3. Koren G, Bologna M, Long D, Feldman Y, Shear NH. Perception of teratogenic risk by pregnant women exposed to drugs and chemicals during the first trimester. *Am J Obstet Gynecol* 1989;160(5 Pt 1):1190-4.

4. Mazzotta P, Magee LA, Maltepe C, Lifshitz A, Navioz Y, Koren G. The perception of teratogenic risk by women with nausea and vomiting of pregnancy. *Reprod Toxicol* 1999;13:313-9.

5. Csajka C, Jaquet A, Winterfeld U, Meyer Y, Einarson A, Panchaud A. Risk perception by healthcare professionals related to drug use during pregnancy: a Swiss survey. *Swiss Med Wkly* 2014;144:w13936.

6. Sanz E, Gomez-Lopez T, Martinez-Quintas MJ. Perception of teratogenic risk of common medicines. *Eur J Obstet Gynecol Reprod Biol* 2001;95:127-31.

7. Damase-Michel C, Pichereau J, Pathak A, Lacroix I, Montastruc J. Perception of teratogenic and foetotoxic risk by health professionals: a survey in Midi-Pyrenees area. *Pharm Pract* 2008;6:15-9.

8. Cantilino A, Lorenzo L, Paula Jdos A, Einarson A. Use of psychotropic medications during pregnancy: perception of teratogenic risk among physicians in two Latin American countries. *Rev Bras Psiquiatr* 2014;36:106-10.

9. Frost Widnes SK, Schjott J. Drug use in pregnancy—physicians' evaluation of quality and clinical impact of drug information centres. *Eur J Clin Pharmacol* 2009;65:303-8.

10. RELIS. Årsrapport 2015 (annual report 2015). p. 13. Available at: <http://www.relis.no/multimedia/155/Arsrapport-2015.pdf>. Accessed August 16, 2016.

11. Polifka JE, Faustman EM, Neil N. Weighing the risks and the benefits: a call for the empirical assessment of perceived teratogenic risk. *Reprod Toxicol* 1997;11:633-40.

12. Heaman M, Gupton A, Gregory D. Factors influencing pregnant women's perceptions of risk. *MCN Am J Matern Child Nurs* 2004;29:111-6.

13. Petersen I, McCrea RL, Lupattelli A, Nordeng H. Women's perception of risks of adverse fetal pregnancy outcomes: a large-scale multinational survey. *BMJ Open* 2015;5:e007390.

14. Thurmann PA. Safety and risk communication to patients. *Expert Opin Drug Saf* 2006;5:747-50.

15. Koren G, Sakaguchi S, Klieger C, et al. Toward improved pregnancy labelling. *J Popul Ther Clin Pharmacol* 2010;17:e349-57.

16. Escitalopram. Consumer drug information [Internet]. Available from: <https://www.drugs.com/cdi/escitalopram.html> (Last date of review, Aug. 8, 2016). Accessed August 16, 2016.

17. Widnes SF, Schjott J, Granas AG. Risk perception and medicines information needs in pregnant women with epilepsy—a qualitative study. *Seizure* 2012;21:597-602.

18. Lupattelli A, Spigset O, Bjornsdottir I, et al. Patterns and factors associated with low

adherence to psychotropic medications during pregnancy—a cross-sectional, multinational web-based study. *Depress Anxiety* 2015;32:426-36.

**19.** Høye S, Straand J, Brekke M. [How do general practitioners keep up to date on pharmacotherapy?]. *Tidsskr Nor Lægeforen* 2008;128:2692-5.

**20.** Slovic P, Fischhoff B, Lichtenstein S. Why study risk perception? *Risk Anal* 1982;2:83-93.

**21.** Duggan L, McCarthy S, Curtis LM, et al. Associations between health literacy and beliefs about medicines in an Irish obstetric population. *J Health Commun* 2014;19(Suppl 2):106-14.

**22.** Lupattelli A, Picinardi M, Einarson A, Nordeng H. Health literacy and its association with perception of teratogenic risks and health

behavior during pregnancy. *Patient Educ Couns* 2014;96:171-8.

**23.** Koren G. The way women perceive teratogenic risk. *Can J Clin Pharmacol* 2007;14:e10-6.

**24.** Pole M, Einarson A, Pairedeau N, Einarson T, Koren G. Drug labeling and risk perceptions of teratogenicity: a survey of pregnant Canadian women and their health professionals. *J Clin Pharmacol* 2000;40:573-7.

**25.** Jasper JD, Goel R, Einarson A, Gallo M, Koren G. Effects of framing on teratogenic risk perception in pregnant women. *Lancet* 2001;358:1237-8.

**26.** Cox AR, Butt TF. Adverse drug reactions: when the risk becomes a reality for patients. *Drug Saf* 2012;35:977-81.

**27.** Bramley D, Mohandas C, Soor S, Erskine D, Osborne C. Does a medicines information service have a positive impact on patient care? *Pharmaceutical J* 2009;282:139-40.

**28.** Hedegaard U, Damkier P. Problem-oriented drug information: physicians' expectations and impact on clinical practice. *Eur J Clin Pharmacol* 2009;65:515-22.

**29.** Bakkebo T, Widnes SF, Aamlid SS, Schjott J. Physicians' perception of teratogenic risk and confidence in prescribing drugs in pregnancy—influence of Norwegian drug information centers. *Clin Ther* 2016;38:1102-8.

**30.** Wilmer E, Chai S, Kroumpouzos G. Drug safety: pregnancy rating classifications and controversies. *Clin Dermatol* 2016;34:401-9.