ARTICLE DETAILS

TITLE (PROVISIONAL)	Medicines information needs during pregnancy – A multinational comparison
AUTHORS	Hämeen-Anttila, Katri; Jyrkka, Johanna; Enlund, Hannes; Nordeng, Hedvig; Lupattelli, Angela; Kokki, Esa

VERSION 1 - REVIEW

REVIEWER	Per Damkier M.D., Ph.D. Head Consultant Department of Clinical Chemistry & Pharmacology Odense University Hospital Denmark COI statement: I declare no conflicts of interest.
REVIEW RETURNED	30-Jan-2013

THE STUDY	Introduction Clear and well-written.
	Methods Design The authors refer on several occasions and on key issues to a general description of the study design, to an unpublished reference. This is will not do.
	Statistics Table 1 has age described by mean and SD. While the number of subjects to some (but not for all strata) extent justify this, I strongly suggest that the representation be mean and interpercentile ranges. Limitations While the authors do acknowledge the selection bias, I clearly feel that they place too little emphasis on this main weakness of the study. There is no real discussion the possible impact on the results and the external validity of these data.
	References Reference 10: Unpublished. As such not permissable as a reference, especially given the context (details on study population and methods) Reference 1 is somewhat old on this subject; much data are available from more recent papers.
RESULTS & CONCLUSIONS	Results While the overall number of respondents is reasonably impressive, I feel that some perspective is warranted. An estimate of the number of possible respondents would be of some help in assessing the degree to which these data can be extrapolated; i.e. a rough

estimate of total eligible study population (surely available for national registers on birth-rates) for each country. Additionally, some quantitative assement of the number of unique users accessing the first web-page should be available (unless the result reported actually reflect this (somewhat unclear) which would mean that 98.6% of every web-page hit resulted in an active participant). I would suggest that a very clear description be made of this and that such data be part of a revised figure 1. Additionally, I find the age range worthy of a comment as 15 and 54 are rather extreme outliers (if not totally implausible) for the intended study population. Maybe some age-related censoring of data should be discussed?

Discussion

The structure of the discussion appears somewhat unsystematic; p12 l19 starts out with discussing implications of the findings; I would suggest that the Authors first discuss their findings in the perspective of other relevant studies ass well as strength and weaknesses (see below) of their study

While the authors do acknowledge the selection bias, I clearly feel that they place too little emphasis on this main weakness of the study. There is no real discussion the possible impact on the results and the external validity of these data. It is hardly surprising that 50-70 per cent of pregnant women, actively accessing an internet questionnaire on the need for information on drug use during pregnancy, indicates a "need for information". The argumentation (pp13 line55ff) is rather weak as it is surely a stretch to assume that "high internet penetration rates" attenuates the selection bias of women actively seeking out information on drugs during pregnancy?

P13 line 43 :no need to repeat this statement: identical to p12 line 5.

Conclusion
I would advocate for a short separate heading with a short and concise conclusion that reflects the data and the limitations of the method applied.

REVIEWER	Margareta Larsson
	Associate professor
	Dep of Women's and Children's Health
	Uppsala University
	Sweden
	I have no competing interests
REVIEW RETURNED	08-Feb-2013

GENERAL COMMENTS	This is a cross-sectional study using web based questionnaires to investigate information about medical products among pregnant women in 18 countries. The sample size is big which is a strength but is likely to be biased by the methodology used.
	I have the following comments and suggestions:
	I lack a definition what is meant by medicines. It is a very broad concept. Looking into the literature review other researchers have used different terminology, such as drugs, medication, prescription drugs etc. The question used in the survey was likewise unspecific so women may have understood the word medicine in various ways. This needs to be clarified and also discussed as a limitation.
	In the abstract the word international is used. However countries

	from Asia and Africa are lacking. Please use another expression than international. Industrialized countries on line 44 p 4 is also a problematic concept which I would advise you to avoid.
	Materials and methods
	Explain the rationale for including those 19 countries. Any calculation of power? Why the choice of two months?
	The main outcome measures are two questions but the result section as well as Table 1 also includes USE of medicines and women were given a list of medicines to choose from. This is not mentioned in the method section and is not part of the aim of the study. Either this should be included in aim and method or removed from result or perhaps moved to the method section when presenting the study population.
	The representativeness of the study population is a main issue for judgment of the validity of the study and needs to be included at least in brief.
	Results
	Generally the term medicine is used except on p 7 line 55 where you specify OTC. Why is that?
	Discussion
	There are some more studies on use of the Internet as information source by pregnant women, where also the issue of how women perceive the trustworthiness is presented and discussed. Media literacy may have increased over time but there may still be a need for health care providers to engage in discussions about what information sources their clients use. Those studies could be part of the discussion. I personally question that health personnel should devote too much of their precious time to be involved and available on the Internet. This is an overwhelming task and health care providers in general may not have enough time or skills to do so. Discuss also the lack of a precise definition of the term medicine.

VERSION 1 – AUTHOR RESPONSE

Reviewer: Per Damkier
M.D., Ph.D.
Head Consultant
Department of Clinical Chemistry & Pharmacology
Odense University Hospital
Denmark

COI statement:
I declare no conflicts of interest.

Introduction
Clear and well-written.

Methods
Design
The authors refer on several occasions and on key issues to a general description of the study design, to an unpublished reference. This is will not do.

Answer:
We have added more information about the representativeness of the study population in Table 1. Overall, our study populations were assessed as closely representative of the target populations in each participating country with respect to maternal age, parity and educational level. We have also elaborated on this issue in the discussion.

Statistics
Table 1 has age described by mean and SD. While the number of subjects to some (but not for all strata) extent justify this, I strongly suggest that the representation be mean and interpercentile ranges.

Answer:
SD have been changed to interpercentile ranges.

Limitations
While the authors do acknowledge the selection bias, I clearly feel that they place too little emphasis on this main weakness of the study. There is no real discussion the possible impact on the results and the external validity of these data.

Answer:
We acknowledge that this is an important issue. Epidemiological studies on web-based recruitment method have shown such recruitment valid (van Gelder 2010, Huybrechts 2010, Ekman 2006). Moreover, women in childbearing age represent the age group with higher rate of internet utilization. And as we stated in the discussion, internet penetration rates are very high in households and working environments in the participating countries. Thus, we believe that the level to which these findings can be extrapolated should be based on the representativeness of the respondents to the general birthing populations in each country. Overall, our study populations were assessed as closely representative of the target populations in each participating country (see Table 1). We have added these points to the Discussion -section.

References
Reference 10: Unpublished. As such not permissable as a reference, especially given the context (details on study population and methods)
Reference 1 is somewhat old on this subject; much data are available from more recent papers.

Answer:
We have deleted the unpublished reference and added more information about the representativeness of the study population in Table 1.
Reference 1 has been changed to a more recent one.

Results
While the overall number of respondents is reasonably impressive, I feel that some perspective is warranted. An estimate of the number of possible respondents would be of some help in assessing the degree to which these data can be extrapolated; i.e. a rough estimate of total eligible study population (surely available for national registers on birth-rates) for each country. Additionally, some quantitative assement of the number of unique users accessing the first web-page should be available (unless the result reported actually reflect this (somewhat unclear) which would mean that 98.6% of every web-page hit resulted in an active participant). I would suggest that a very clear description be made of this and that such data be part of a revised figure 1.

Answer:

We agree that this is a relevant consideration. Unfortunately, we do not have information on how many women saw the study invitation online and closed the internet page without clicking "yes" or "no" to the question "are you willing to participate in the study", since the Questback program cannot provide such information. Furthermore, we do not know how many user accesses are expected to occur per year (or month) in each of the website used. We used pregnancy forums and social networks, so this information would not be completely useful anyhow.

We believe that the level to which our findings can be extrapolated should be based on the characteristics of our study participants, and how close these are to the characteristics of the general birthing populations in each country. As stated above, we have added more information about the representativeness of the study population in Table 1 and in the discussion.

Additionally, I find the age range worthy of a comment as 15 and 54 are rather extreme outliers (if not totally implausible) for the intended study population. Maybe some age-related censoring of data should be discussed?

Answer:
In our study, 4 women were 15-years-old and 5 were 16-years-old. Among those with 15 years of age, 1 is from Sweden, 1 from USA, 1 from Uruguay and 1 from Poland. Among those with 16 years of age, 1 was from Canada, 2 from Sweden and 2 from the UK. Only 1 woman was 54 (from the USA). There is no one between 51 and 53. The role played by these isolated cases, especially the woman aged 54 years, is not so relevant when the mean age is calculated. With respect to teen pregnancies, the following should be considered: In North and South America the prevalence of teen pregnancies is quite relevant, as also addressed by the CDC (http://www.cdc.gov/teenpregnancy/). Exclusion of young women from the study population would not reflect the characteristics of the target population in some of the countries analyzed. Furthermore, the mean age at birth for our study populations - in each individual country – is very close to the mean age of the general birthing populations, suggesting satisfactory external validity of our findings.

Discussion

The structure of the discussion appears somewhat unsystematic; p12 l19 starts out with discussing implications of the findings; I would suggest that the Authors first discuss their findings in the perspective of other relevant studies ass well as strength and weaknesses (see below) of their study

Answer:
We have changed the order of the discussion section as suggested.

While the authors do acknowledge the selection bias, I clearly feel that they place too little emphasis on this main weakness of the study. There is no real discussion the possible impact on the results and the external validity of these data. It is hardly surprising that 50-70 per cent of pregnant women, actively accessing an internet questionnaire on the need for information on drug use during pregnancy, indicates a "need for information". The argumentation (pp13 line55ff) is rather weak as it is surely a stretch to assume that "high internet penetration rates" attenuates the selection bias of women actively seeking out information on drugs during pregnancy?

Answer:
More in-depth discussion about the selection bias and external validity has been added to the discussion.

P13 line 43 :no need to repeat this statement: identical to p12 line 5.

Answer:
Statement has been deleted.

Conclusion
I would advocate for a short separate heading with a short and concise conclusion that reflects the data and the limitations of the method applied.

Answer:
Conclusions have been added.

Reviewer: Associate professor
Margareta Larsson
Dep of Women's and Children's Health
Uppsala University
Sweden
I have no competing interests

This is a cross-sectional study using web based questionnaires to investigate information about medical products among pregnant women in 18 countries. The sample size is big which is a strength but is likely to be biased by the methodology used.
I have the following comments and suggestions:
I lack a definition what is meant by medicines. It is a very broad concept. Looking into the literature review other researchers have used different terminology, such as drugs, medication, prescription drugs etc. The question used in the survey was likewise unspecific so women may have understood the word medicine in various ways. This needs to be clarified and also discussed as a limitation.
In the abstract the word international is used. However countries from Asia and Africa are lacking. Please use another expression than international. Industrialized countries on line 44 p 4 is also a problematic concept which I would advise you to avoid.

Answer:
The following description on how medicines were asked has been added to the methods section:
"Standardized questions about maternal factors were posed to the subjects, with emphasis on presence of acute and long-term illnesses during pregnancy. In affirmative case, women were questioned about medication use for each individual indication as free-text entry."

Furthermore we spesifically asked about use of over-the-counter (OTC) medications and used a list of five OTC categories, namely painkillers, nasal drops, antinauseants, antacids and laxatives along with examples of brand name products of relevance in the concerned country to aid recall.

In our dataset, a medication was defined as single product containing one or more active ingredients. Whenever the study subjects reported specific trademark names of medications, we firstly identified the main active ingredient(s) and formulation of the branded medicinal product either in the relevant national medicine database or in Martindale database. Secondly, we coded all recorded medications into the corresponding ATC codes in accordance with the WHO ATC system. Medicinal products were coded into the ATC 5th level, whenever possible, otherwise higher levels (i.e. 2nd- 4th) could be utilized, if appropriate. In those instances where unspecified medications within a drug class were reported, we either utilized ATC codes above the 5th level (e.g. antidepressants were coded as "N06A") or generic codes created ad hoc for our classification system (e.g. medications for sleeping problems were coded as "E000020"). The OTC status of the medications reported was cross-checked

with the prescription policies within each participating country. Whenever a prescription medication was reported under the OTC question, such record was omitted from the analysis of OTC use and accounted for in the estimation of overall medication use. Iron, supplements, vitamins, minerals, herbal remedies and any type of alternative medicine were excluded from the estimation of medication use".

The term "international" has been deleted from the text and the term "multinational" used, when relevant. The term "industrialized" has also been deleted.

Materials and methods
Explain the rationale for including those 19 countries. Any calculation of power? Why the choice of two months?

Answer:
Member countries of Teratology Information Service network, i.e. ENTIS in Europe, OTIS in North and South America and Mothersafe in Australia, were invited to take part in the project. Of these, the following countries agreed to take part in the project and conduct the study: Norway, Sweden, Finland, Iceland, Italy, France, the United Kingdom, Austria, Switzerland, the Netherlands, Poland, Slovenia, Croatia, Serbia, Russia, the USA, Canada, Australia and South America. This has been added to the methods section.

We chose two months because previous experiences with web-based study indicate that very high level of response at the beginning of the study (Nordeng et al. Eur J Clin Pharmacol 2010) as soon as the study invitation is posted on the websites. After a couple of weeks, the number of responses starts decreasing. Further, economical reasons forced us to limit the recruitment phase to 2 months.

As this was a descriptive study, no power calculations were performed.

The main outcome measures are two questions but the result section as well as Table 1 also includes USE of medicines and women were given a list of medicines to choose from. This is not mentioned in the method section and is not part of the aim of the study. Either this should be included in aim and method or removed from result or perhaps moved to the method section when presenting the study population.

Answer:
Originally, the use of OTC medicines was put to the manuscript to show a context where need for medicines information occur. But we agree with the reviewer that the aim of this study is not to study medicines use and the use of OTC medicines has now been deleted from the manuscript.

The representativeness of the study population is a main issue for judgment of the validity of the study and needs to be included at least in brief.

Answer:
We have added more information about the representativeness of the study population in Table 1.

Results
Generally the term medicine is used except on p 7 line 55 where you specify OTC. Why is that?

Answer:
The use of OTC medicines has now been deleted from the manuscript.

Discussion

There are some more studies on use of the Internet as information source by pregnant women, where also the issue of how women perceive the trustworthiness is presented and discussed. Media literacy may have increased over time but there may still be a need for health care providers to engage in discussions about what information sources their clients use. Those studies could be part of the discussion. I personally question that health personnel should devote too much of their precious time to be involved and available on the Internet. This is an overwhelming task and health care providers in general may not have enough time or skills to do so.

Discuss also the lack of a precise definition of the term medicine.

Answer:

We agree. We have added several new references (ref 6–9) and more discussion about the Internet as an information source by pregnant women and how women perceive the trustworthiness. Furthermore, we state a need that health care professionals should be engaged in discussions about what information sources their patients use.

We have moderated our statement about the health care professionals' involvement in the Internet and social media, because that's where the people seek information nowadays. This does not diminish the role of the face-to-face meetings with patients in clinical practice. Furthermore, the professionals working in the social media may be different from the ones who see patients in daily practice.

VERSION 2 – REVIEW

REVIEWER	Per Damkier M.D., Ph.D. Head Consultant, Clinical Pharmacology Department of Clinical Chemistry & Pharmacology Odense University Hospital Denmark COI statement I declare no conflicts of interest.
REVIEW RETURNED	22-Mar-2013

GENERAL COMMENTS	The authors has addressed the issues stated in the review to a satisfactory degree. The resubmitted manuscript is substantially improved.