Drug information in pregnancy

Attitudes and needs among pregnant women and physicians

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Abbreviations

ACE	Angiotensin-Converting Enzyme
AED	Antiepileptic Drug
ARB	Angiotensin Receptor Antagonist
ATC	Anatomical Therapeutic Chemical [classification system]
BMQ	Beliefs about Medicines Questionnaire
DIC	Drug Information Centres
FDA	Food and Drug Administration
FK	Felleskatalogen (Norwegian product monographs)
GEE	Generalized Estimating Equations
GP	General Practitioner
HP	Hospital Physician
NSAID	Non-Steroidal Anti-inflammatory Drug
OTC	Over-The-Counter [drugs]
PDD	Prescription Drug Database
PDR	Physicians' Desk Reference
PIL	Patient Information Leaflet
RELIS	Regional Medicines Information and Pharmacovigilance Centres in Norway
SIMS	Satisfaction with Information about Medicines Scale
SPC	Summary of Product Characteristics
SSRI	Selective Serotonin Reuptake Inhibitor
TIS	Teratology Information Services
WHO	World Health Organization
WWE	Women With Epilepsy

Abstract

Background: Drug use in pregnancy is common and both pregnant women and their physicians are in need of appropriate information for decision-making regarding drug therapy. However, uncertainty about the risks of drug use in pregnancy could result in restrictive attitudes to prescribing medicines and to their use.

Purpose: To examine attitudes of and needs for medicines information among pregnant women and physicians.

Materials and methods: Four studies based on three different methods were included; **I:** a descriptive study comparing drug advice regarding pregnancy from two commonly used sources: the Norwegian Drug Information Centres (DICs, named RELIS) and the product monographs in Felleskatalogen (FK), **II**: a survey among physicians who consulted RELIS for information on patient-specific drug use during pregnancy, **III**: interviews of pregnant women with epilepsy (WWE) using antiepileptic drugs (AEDs), **IV**: a survey among women attending ultrasound examination in gestation weeks 17-19 and their respective general practitioners (GPs).

Results: Commonly used sources of information differed in advice regarding drug use in pregnancy. RELIS was a valued service among physicians and most advice had a clinical impact on therapeutic decisions. Pregnant WWE were confident in using AEDs through communication with their neurologist, but were concerned about dose adjustments. Pregnant women had higher teratogenic risk perceptions and lower confidence in use of medicines compared to their GPs. Phrasing of information texts may have influenced teratogenic risk perceptions.

Conclusions and further implications: Deciding whether or not to prescribe or use medicines in pregnancy may be influenced by teratogenic risk perceptions, phrasing of medicines information, differences in advice between sources of information and availability of patient-specific and producer-independent medicines information. Physicians should aim to tailor the information to the pregnant woman's risk perception level and desire for information.

List of publications

Paper I Frost Widnes SK, Schjøtt J. Advice on drug safety in pregnancy: are there differences between commonly used sources of information? Drug Saf 2008; 31(9):799-806.

Paper II Frost Widnes SK, Schjøtt J. Drug use in pregnancy - physicians' evaluation of quality and clinical impact of drug information centres. Eur J Clin Pharmacol 2009; 65(3):303-8.

Paper III Widnes SF, Schjøtt J, Granas AG. Risk perception and medicines information needs in pregnant women with epilepsy – a qualitative study. Seizure 2012; 21(8): 597–602.

Paper IV Widnes SF, Schjøtt 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 Mar 29. [Epub ahead of print]. DOI 10.1007/s40264-013-0035-9.

Contents

1. INTRODUCTION

1.1. Use of drugs in pregnancy

Pregnant women, like women in general, use drugs to manage chronic diseases and to treat acute or pregnancy-induced symptoms (1). Based on results from drug utilization studies performed during the last 15 years, medication exposure during pregnancy is common, with frequencies varying from 39 - 99% (2-21). Table I provides an overview of studies published between 1999 and 2012, stating frequency of drug use and the most commonly used medicines. The drug utilization studies were performed solely in Western countries, and the studies reveal large variations in findings regarding frequency of drug use and the type of drugs used. This result may be related to differences in methodology, as well as country-specific differences (22). Furthermore, methodology has changed over time. Interviews or questionnaire surveys, with limited sample size, were commonly used methods in studies performed in the seventies and eighties (22, 23). Prescription drug databases (PDD) have become more common in drug utilization studies from 2000 onwards. Such studies provide opportunities for large sample sizes, but will not include use of over-the-counter (OTC) drugs, and do not measure actual drug use (24).

Use of herbal medicines is also frequent among pregnant women (25-28) and they are often used without informing the physician (27). In Norway, the herbal medicines most commonly used by pregnant women are ginger, cranberry and raspberry leaf (26, 27). Significantly, the documentation on safety of herbal medicines in pregnancy is even more limited than for modern medicines and, considering the sparse documentation on their effects, use of herbal medicines can seldom be recommended in pregnancy (26).

Table I. Overview of studies examining frequency of drug use in pregnancy (1999-2011).

Frequency of drug use	Period included in frequency	Most commonly used drugs	N	Drug history obtained	First Author	Year	Country
39 %	P*	Antibiotics, Anti-infective gynecological drugs, ophtalmologics	2041	Interview	Olesen (2)	2001	Denmark
44 %	3 + P + 3	Antibiotics, gynaecological drugs, anti-asthmatics	16001	PDD	Olesen (3)	1999	Denmark
46 %	P	Antibiotics, gynaecological anti-infective agents, nasal preparations	43470	PDD	Malm (4)	2003	Finland
56 %	P	Anti-infectives, respiratory drugs, gastrointestinal drugs	1945	Interview	Nordeng (5)	2001	Norway
56 %	P	Antibiotics, analgesics, anti-asthmatics	1626	Medical records from a cohort	Riley (6)	2005	USA
58 %	3 + P + 3	Antibacterials, sex hormones, NSAIDs	102995	PDD	Stephansson (7)	2011	Sweden
64 %	3 + P	Anti-infectives, respiratory drugs, opioid and nonopioid analgesics	152531	PDD	Andrade (8)	2004	USA
70 %	3 + P	Iron supplements, amoxicillin, progesterone	33343	PDD	Gagne (9)	2008	Italy
75 %	P	Haematological drugs, nutritional drugs, tocolytics	9004	Interview	Donati (10)	2000	Italy
79 %	P	No data	5412	PDD	Bakker (11)	2006	The Netherlands
83 %	3 + P + 3	Sex hormones, penicillins, cough and cold preparations	106329	PDD	Engeland (12)	2007	Norway
83 %	P	Analgesics, anti-infectives, antacids.	11545	Questionnaire	Headley (13)	2004	UK
84 %	P	Paracetamol, drugs against heartburn, penicillins	1793	Questionnaire	Nordeng (14)	2010	Norway
85 %	3 + P	Antacids, antibacterials, oral iron	3937	PDD	Irvine (15)	2010	Scotland
93 %	P	Prenatal vitamins, paracetamol, calcium carbonate	578	Interview	Glover (16)	2003	USA
94 %	P	Drugs acting on the alimentary tract and metabolism (ATC group A), genito-urinary system and sex hormones (group G), nervous system (group N)	911	Prescription data and questionnaires	Beyens (17)	2003	France
96 %	P	Drugs acting on the alimentary tract and metabolism (ATC group A), nervous system (ATC-group N), blood and blood forming organs (group B)	23898	PDD	Crespin (18)	2011	France
96 %	P	Drugs acting on the alimentary tract and metabolism (ATC group A), blood and blood forming organs (group B), genito-urinary system and sex hormones (group G)	41293	PDD	Egen-Lappe (19)	2004	Germany
96-97%	3 + P	Paracetamol-based analgetics, multivitamins, antacids	140	Interview	Henry (20)	2000	Australia
99 %	P	Iron, gastrointestinal drugs, dermatological drugs	1000	PDD	Lacroix (21)	2000	France

PDD; prescription drug database

3 + P + 3; drug history during the period 3 months prior to conception to 3 months after birth

3 + P; drug history during the period 3 months prior to conception to birth

6 + P + 6; drug history during the period 6 months prior to conception to 6 months after birth

P; drug history during pregnancy only, * Purchase of at least one prescription drug during the 120 days before the interview

1.2. Teratogenic drug effects

For all pregnancies, there is a 2 – 4 % baseline risk of major birth defects (29). However, less than 1% of these defects can be attributed to teratogenic effects resulting from maternal drug use (30, 31). The remaining 99% of birth defects have other causes; 9% are thought to be caused by maternal disease such as diabetes, infections or alcohol abuse, 20-25% have a genetic cause, and for the rest (about 65%) the cause is unknown (31).

Teratogens are agents that irreversibly change growth, structure or function of the embryo or fetus, and include viruses, environmental factors, chemicals and drugs (32). Only about 20 drugs or groups of drugs have been proven to be human teratogens (31, 33). Examples of drugs or groups of drugs with established or potential teratogenic effects are given in Table II.

Table II. Examples of drug groups or drugs with potential for teratogenic effects.

Agents acting on the renin-angiotensin system	Estrogens
Antidepressants	Oral contraceptives
Antiepileptic drugs	Retinoids (isotretinoin)
Anti-cancer agents	Carbimazole
Anxiolytics	Lithium
Androgens	Misoprostol
Coumarin derivatives (warfarin)	Thalidomide

From Buhimschi and Weiner (32).

Even for drugs with teratogenic effects, the vast majority of pregnancies with drug exposure will result in normal offspring (33). Drug dose, route of administration, duration of treatment and gestational timing are all determinants for teratogenic risk at drug exposure (34). A drug may be safe at one dosage, but may give teratogenic effects if the dose is increased above a threshold level. Systemic drug exposure is also related to the route of administration. For example, dermal administration will reduce the risk of teratogenic effects due to limited systemic absorption. For drugs with potential for teratogenic effects throughout pregnancy, increased duration of treatment may increase the risks for fetal defects (35).

Timing of exposure, with respect to the different periods in fetal developmental, is an important factor for susceptibility to teratogenic drug effects (35). The time from conception until implantation of the embryo (up to 14 days post conception), is considered to be an “all or none” period, as damage to the embryo will result in either spontaneous abortion or in intact survival. After this period, organogenesis takes place and sensitivity to teratogens is particularly high due to the risk of structural malformations. However, even after organogenesis, fetal growth and organ function may be affected by drug exposure (36, 37). For example, use of Angiotensin-

Converting Enzyme (ACE) inhibitors or Angiotensin Receptor Antagonists (ARBs) in the second or third trimester may induce effects on the fetus such as oligohydramnios and renal failure (38).

1.3. Assessing teratogenic drug effects

Due to the ethical concerns of including pregnant women in randomized controlled clinical trials, drugs have rarely been tested on this population at the time of their introduction into the clinical setting (36). Animal studies on teratogenicity are requested prior to drug approval, but their ability to predict human teratogenicity is limited (37, 39). Assessment of teratogenic risks is therefore based on data that are gradually gathered after drug marketing, through epidemiological studies such as case-control studies, cohort studies or studies of total populations (24, 40), in addition to spontaneous reports of birth defects to pharmacovigilance databases, case reports or case-series (40). An overview of epidemiological study- types and their respective limitations is provided in Table III.

Table III. Overview of types of epidemiological studies used to examine teratogenic drug effects and their respective limitations.

	Examples	Limitations
Cohort studies	**a)** Studies performed by teratology information centres (TIS) (prospective) **b)** Pregnancy registers, based on reports of drug exposure before the outcome is known (prospective) **c)** Pregnancy cohorts, such as The Norwegian Mother and Child Cohort Study (the MoBa study) (prospective)	Misclassification bias Low case numbers obtained Selection bias (loss to follow-up) Confounding by indication
Studies of total populations	**a)** Medical birth registers **b)** Linking of prescription drug databases (PDD) with medical birth registers	Actual drug use or time of drug use is often unknown (PDD) Over-the-counter drugs are not included (PDD) Recall bias in medical birth registers if exposure data are collected after birth Confounding by indication
Case-control studies		Misclassification bias Bias towards reporting known teratogenic effects Recall bias Interviewer bias Low participation rate Confounding by indication

Teratology information services (TIS) perform cohort- studies in which information on drug exposure during pregnancy is collected prospectively (37, 41). Pregnancy registries, established by pharmaceutical companies or independent research groups, prospectively enrol pregnant women with drug exposure. Examples of pregnancy registries are national, regional and international epilepsy and pregnancy registries (42). Pregnancy cohorts, such as the Norwegian Mother and Child Cohort Study (the MoBa study), which included all women giving birth in Norway from 1999 to 2008, can estimate effects of a wide range of exposures during pregnancy. The MoBa study is based on participants' answering questionnaires at several time points during pregnancy and up to 7 years after birth, providing possibilities for long-term follow-up. Questionnaires 1 and 3, filled out in gestation weeks 13-17, and week 30, respectively, ask for medical history and use of medicines in pregnancy (43, 44).

One possibility of studying the total population is to link PDDs with medical birth registers. This results in large data sets; however, it does not provide data on actual drug use (24).

Epidemiological studies have inherent limitations and study results should be interpreted in light of this. A combination of different epidemiological methods may provide the optimal overview of teratogenic risks of drugs (45). Importantly, conclusions on teratogenic causality cannot be drawn from single studies (24, 40) and causality can only be assumed if the frequency of birth defects in children of women using a specific drug significantly exceeds the baseline risk. Furthermore, the number of exposed cases needed to declare a drug free of significant teratogenicity is based on the specificity and frequency of the malformations studied (24, 37), and it is not possible to absolutely establish the risk of drug use in pregnancy (31).

Due to the lack of systematic studies on pregnant women before drug approval, there is a delay in acquiring teratogenic risk information on new drugs (46). A study on drugs approved by the American Food and Drug Administration (FDA) since 1980 found that the mean time for a drug initially classified as having an undetermined teratogenic risk to be assigned a more precise risk was 27 years. This was based on assessments by an expert advisory board. Moreover, the experts were unable to

determine the teratogenic risk of 98% of 172 drugs approved by the FDA between 2000 and 2010 (47).

1.4. Teratogenic risk perceptions

Risk is the probability from 0 – 1 of an event, good or bad, occurring during a certain period of time (48). Risk factors, such as drugs, may contribute to the event, but are not necessarily the cause of the event (49). A perception may be defined as "the way in which something is regarded, understood, or interpreted" (50). It has been suggested that there is a correlation between risk perception and behaviour and that this relationship may vary over time for an individual (51). Furthermore, the concept of attitude consists of three interrelated components; affect, cognition and behaviour (52), indicating that attitudes too may influence risk perceptions and behaviour. The concepts of risk, risk perceptions, attitude and behaviour are therefore of importance for understanding teratogenic risk perceptions.

Dealing with the concept of risk is part of everyday life. However, when pregnancy occurs, managing risks become more complex. Risk perceptions and attitudes also become more evident. The pregnant woman becomes responsible not only for her own well-being and most mothers put the needs of their baby first (53). There are cultural differences in views on pregnancy (54), but Western society's increased focus on risks in pregnancy, including extensive lists of food and activities to be avoided in pregnancy, can lead to a state of hypervigilance and increased anxiety (55).

Only about 1% of birth defects are caused by maternal drug use; however, people generally attribute unrealistically high teratogenic risks to the use of drugs (33). In particular pregnant women, but also health care providers, overestimate teratogenic risks (14, 56-62). For the physician, the consequence may be inadequate treatment of the pregnant woman's acute or chronic disease (62). For the pregnant woman, overestimating teratogenic risks can impact decisions on whether to continue the

pregnancy or not after taking a drug (63), and whether or not to take medicines (64, 65).

So, what are the possible explanations for these unrealistically high teratogenic risk perceptions? The 1960s' discovery of birth defects resulting from use of thalidomide in early pregnancy (the thalidomide tragedy) (66) resulted in an increased awareness of teratogenic effects caused by drug use. This resulted in mandatory systematic developmental toxicity testing of drugs (67), and development of systems for pharmacovigilance (68). It has been suggested that the thalidomide tragedy may be a cause of the increased teratogenic risk perceptions even today (14, 59). Furthermore, the media usually stress the risks related to use of medicines and not the benefits (69)- a factor which could influence attitudes to medicines use in pregnancy. Authorities generally warn against use of alcohol and tobacco during pregnancy (70), and it is possible that pregnant women perceive this to also include use of other exogenous substances, such as drugs. Furthermore, pregnant women's risk perceptions and health decisions are influenced by individual factors, such as experiences and opinions and beliefs of family and friends (64, 71).

One of the physicians' roles is to guide patients in weighing risk and benefits, based on available knowledge (72). The fact that there is scientific uncertainty regarding teratogenic risks of drug use in pregnancy may however increase physicians' own perception of risk (73).

1.5. Principles of drug prescribing in pregnancy

Therapeutic decisions in pregnancy must include balancing the risk of untreated maternal disease against the teratogenic risk of drug treatment (32, 33). However, as 40% of pregnancies are estimated to be unplanned (74), unintended use of medicines in early pregnancy is common. Two different situations requiring counselling of pregnant women regarding drug use are therefore possible:

- Inadvertent exposure to drugs
- Intended continuation or initiation of drug treatment in pregnancy

In either situation, the reason for use of drugs may be a chronic disease (long-term treatment) or acute or pregnancy-related conditions (short-term treatment). However, physicians need to consider the different premises for counselling in the two situations (75). Table IV presents some management principles for the two situations.

Table IV. Management principles of drug therapy in pregnancy.

Inadvertent exposure to drugs	Intended continuation or initiation of drugs
►Obtain accurate details of exposure and gestational age	►Drugs should only be used if the expected benefits (usually to the mother) are greater than the potential risks (usually to the fetus)
►Check for confounding family and personal medical history	►Try to avoid first trimester use
►Obtain up-to-date information about published risks of the drug in humans	►Use drugs that have been used extensively in pregnancy, not new ones
►Emphasize background risk in counselling	►Use the minimum dose required to obtain the desired effect
►Be clear on what is known (absence of data does not equal no risk)	►Absence of data does not imply safety

From Henderson and Mackillop (75).

Planning drug therapy of chronic diseases before conception is important for optimal management in pregnancy (75). Pregnant women with chronic diseases must be informed that withholding treatment may increase maternal and fetal risks, including preterm births, intrauterine growth restrictions and stillbirths (76, 77). For example, in epilepsy, seizures can harm both the mother and her fetus, and this risk must be weighed against the teratogenic risks of antiepileptic drugs (AEDs) (78).

The physiological changes of pregnancy result in several pharmacokinetic changes, such as reduced absorption and increased elimination of drugs. For example, the clearance of lamotrigine may increase to more than 300% of the baseline value by the early third trimester, requiring dose adjustment. Therapeutic drug monitoring before, during and after pregnancy is recommended to evaluate the need for dose adjustments of drugs with pregnancy-altered pharmacokinetics (75).

1.6. Sources of information on drug use during pregnancy

In order to assess teratogenic risks, both pregnant women and physicians need adequate drug information (14, 65, 79). In the following, I will first outline drug information sources available to physicians, and thereafter those available to pregnant women. Drug information to other health care providers or to patients is not covered.

1.6.1. Drug information sources for physicians

A challenge for physicians is access to drug information that is both easily available and useful for counselling pregnant women (80). A lack of such information has been reported (81, 82) . Nonetheless, physicians report use of several sources for information regarding teratogenic drug risks (79, 82, 83). Figure I provides an overview of sources of information relating to drug use in pregnancy that are available to physicians. Some of the sources are presented in the following.

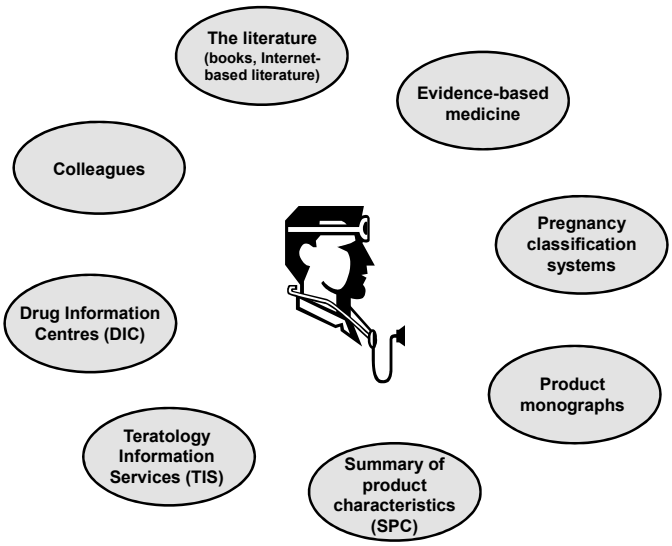

Figure I. Sources of drug information relating to pregnancy that are available to physicians.

1.6.1.1. Product-specific information (SPCs, product monographs)

Pharmaceutical companies are obliged to provide information regarding use in pregnancy in the Summary of Product Characteristics (SPC) and Patient Information Leaflet (PIL). Product monographs are based on the information in the SPC and are intended as practical guidelines for clinical use. Examples of product monographs include the Physician's Desk Reference (PDR) in the USA, and Felleskatalogen (FK) in Norway. Because of the lack of clinical trial- data on pregnant women, the regulations set by medical authorities as well as fears of litigation, product-specific information rarely states that a medicine is safe to use in pregnancy (84). Consequently, in these sources a contraindication in pregnancy does not always reflect an established teratogenic risk. Therefore, product-specific information sources are not suited for counselling patients regarding teratogenic risks. If they are consulted as the primary source, physicians may fail to prescribe necessary medicines (76, 85). To illustrate this, Figure II presents a comparison between the SPC-text regarding use in pregnancy of a 2nd generation antihistamine, loratadine (Clarityn TM) (86, 87), and a summary made by the Norwegian Drug Information Centres (DICs) regarding antihistamines for allergic rhinitis during pregnancy (88).

Summary of product characteristics (SPC) for loratadin (Clarityn TM) **(86,87).**

Loratadine was not teratogenic in animal studies. The safe use of loratadine during pregnancy has not been established. The use of Clarityn Allergy Tablets during pregnancy **is therefore not recommended.**

RELIS *(Norwegian Drug Information Centres).* ***Safe medicines for pregnant and breast feeding women with allergic rhinitis*** *(88).* *(translated text)*

The clinical experience with use of 2nd generation antihistamines among pregnant women is now extensive. This experience **does not indicate increased teratogenic risks.**

Figure II. Texts regarding risks in pregnancy from a product-specific source (left) and a producer-independent source (right).

As can be observed in the Figure, the product-specific source is restrictive regarding use in pregnancy, while the producer-independent source states safe use based on extended experience. This illustrates the possible consequences of utilizing only product-specific information for counselling pregnant women.

1.6.1.2. Teratogen information services (TIS) and Drug information centres (DIC)

TIS and DICs are available to health care providers in many countries worldwide. Both TIS and DIC aim to provide problem-oriented drug information, i.e. discussion of a specific patient problem rather than purely report findings from the literature. The information is generally provided by clinical pharmacologists, pharmacists or specialists in teratology, and the working method is similar to the concept of evidence-based medicine (89, 90).

The difference between DIC and TIS is that TIS is specialized for counselling teratogenic risks (76, 91, 92) while drug queries to DIC are not confined to pregnancy and lactation. DICs mainly provide services to health care providers, but in some countries also to the lay public (93, 94). TIS usually serve both health care providers and the public (92). In countries where a TIS is not established, questions regarding pregnancy are usually handled by DICs, which frequently receive questions on this topic (89, 95-98). In Norway, DIC (RELIS) was established in 1994 and questions from health care providers regarding drug use in pregnancy are answered by RELIS.

Important consequences of advice provided by TIS have been documented. This includes prevention of congenital malformations and unnecessary pregnancy terminations, as well as a reduction of unrealistic concerns related to drug use (99). Correspondingly, the DIC services have been found to have an impact on clinical practice (89, 90, 93, 98, 100).

1.6.1.3. Pregnancy risk classification systems

Some countries, for example USA, Australia and Sweden, have introduced pregnancy risk classification systems for drugs. The intention is to categorize drugs according to their teratogenic risks in order to guide physicians in their risk/benefit evaluation regarding drug prescription (34, 101). The systems are set up by teratologists, gynaecologists and clinical pharmacologists (101). However, limitations with these classification systems have been identified. For example, 70% of medicines in the American FDA system are allocated to the same risk category (84); the systems do not distinguish between animal and human data (1); and there are major inconsistencies between different classification systems (34, 101). Due to these shortcomings, the FDA pregnancy labelling system is currently changing to a narrative model that includes three elements: risk summary, clinical considerations and data (1, 84). This model is similar to that of the Swedish online database "Drugs and Birth Defects" (102).

1.6.2. Drug information sources for pregnant women

Patients are encouraged to take an active role in their own health care and participate in therapeutic decisions (103, 104), implying a need for access to appropriate medicines information. In line with this, pregnant women report needs for information about teratogenic risks of medicines (14, 65). They also report use of several medicines information sources (14, 105, 106) as presented in Figure III. Some of the sources are presented in the following.

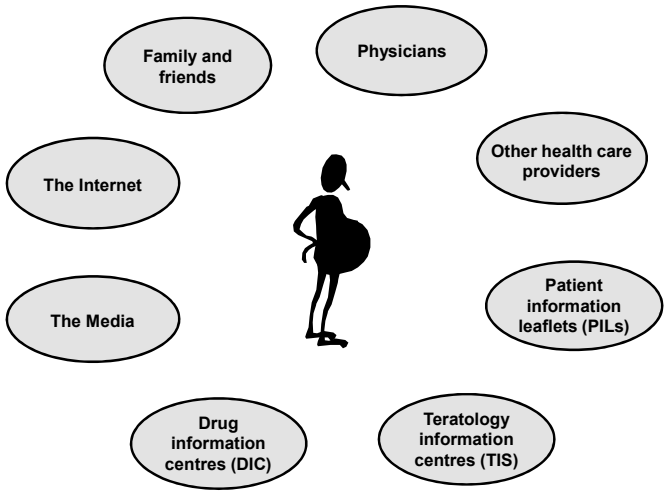

Figure III. Sources of drug information relating to pregnancy that are available to pregnant women.

1.6.2.1. Health care providers

The physician and the pharmacist have important roles as providers of medicines information. Other health care providers have no such formal roles or expertise, and this section therefore focuses on physicians and pharmacists as sources of information. It should however be mentioned that midwives are commonly utilized as a source of general health information by pregnant women, and might therefore be consulted for advice regarding medicines use. No studies examining midwives' attitude to medicines use during pregnancy have been identified, although others have found that midwives support use of complementary and alternative medicine, such as herbal medicines, during pregnancy (107).

Studies have shown that pregnant women consider their physician to be an important source of drug information (65, 105). This implies possibilities for tailoring information according to individual needs, which can increase patient satisfaction and adherence to treatment (108). Furthermore, establishing trust in the patient-physician relationship may increase pregnant women's confidence in physicians' advice regarding drug therapy (105).

Community pharmacists are easily accessible for advice regarding drug related-issues, including drug use in pregnancy (14). However, studies have found that community pharmacists do not always provide evidence-based or appropriate advice to pregnant women, and they frequently refer patients to their physicians without providing advice themselves (109-111). This may indicate inexperience in dealing with pregnancy-related drug information, or lack of appropriate sources of information. This type of counselling may therefore have potential for improvement.

It should also be pointed out that physicians and pharmacists have different roles regarding provision of medicines information. The physician is the prescriber, making therapeutic decisions by interacting with the patient. Pharmacists are the medication specialists and should provide additional information when prescribed medicines are dispensed. They should ideally should support and complement the advice provided by the physician. A further role for pharmacists is to provide advice regarding use of OTC drugs to treat mild symptoms (109). Utilization of the complementary roles of physician and pharmacist could result in better provision of medicines information to pregnant women.

1.6.2.2. Patient information leaflets (PILs)

PILs, accompanying each medicine pack, aim to inform patients on how to use the medicine. The PIL should be based on the SPC and the text should be phrased so that patients understand the content (103, 112). The PIL is the only written information every patient is guaranteed to receive about their medicines (113, 114) and is often the only source available when the patient actually takes the medicine (103).

The PIL should contain information regarding risks at pregnancy and lactation (115, 116). However, as in SPCs and product monographs, use in pregnancy is rarely recommended due to the inherent limitations of establishing teratogenic risks (84), as illustrated with antihistamines in Section 1.6.1.1. In one focus- group study, the participating pregnant women stated that PILs are not useful as an information source due to vague texts such as “as far as it is known this drug can be used during

pregnancy" or "ask your physician" when the drug had already been prescribed by one. The consequence of such text formulations could be concerns that the drug is harmful (65).

1.6.2.3. The Internet and media

The Internet is frequently used by pregnant women in search of health-related information (106, 117, 118) and the number of websites containing such information is increasing (119). There are numerous commercial Norwegian Internet- sites that target pregnant women, and several of them offer opportunity to exchange experiences with others through discussion forums, for example "barnimagen.no" (120), "mammanett.no" (121) and "snartmamma.com" (122). There are also government-funded websites providing information to pregnant women (123), however, there is currently little information available on these websites.

Pregnant women's reported reasons for use of the Internet are search for general pregnancy information, and additional information to that already provided by health care providers (106), and that it is a quick and convenient source of information (117). Furthermore, some pregnant women report dissatisfaction with information or lack of time to discuss the matter with health care providers (106). In one study, half of the participating women reported that they used information on the Internet in decision-making regarding pregnancy (106).

An important limitation of Internet information is that data may be inaccurate or incomplete. Consequently, it may be difficult for patients to distinguish between websites of high and low quality (117). Although some pregnant women perceive health information on the Internet to be reliable (118), other studies have highlighted the problem of patients' evaluation of the quality of information on websites, and the risk of receiving incorrect information (106, 117). As a result, many pregnant women report that they are confused by the information found on websites (117).

The increasing use of the Internet as an information source influence patient-physician relationships. Physicians may utilize this by guiding Internet- informed

patients to reliable and accurate websites (119, 124). This may result in patients becoming more empowered to make informed health care choices (119).

The media, including social media such as Facebook and Twitter, contribute to peoples' general knowledge and judgement of medical treatment. However, the media's tendency to focus on negative drug-related effects and its search for sensationalism could have a substantial impact on pregnant women's concerns about drug use (69, 76). A review article showed that studies with "positive" results, i.e. revealing an increased risk for teratogenic effect with a drug, are more likely to be cited in the medical literature than studies with "negative" results, i.e. not showing adverse effects on the fetus (125). Such citation bias is easily transferred to the lay media and, in general, drug warnings are cited by the media while the benefits of medicines use in pregnancy may not receive the same attention (69, 126). A further example of the impact of the media was the 2005 publication of a study that found increased risks for cardiac malformations in children whose mothers had taken the SSRI paroxetine in early pregnancy. Following the vast media- coverage of this study, one TIS documented an immediate increase in calls from concerned women taking or planning to take paroxetine (69).

1.6.2.4. TIS and DIC

As also described in Section 1.6.1.2, TIS and DIC are available to pregnant and breast-feeding women in some countries. TIS have been shown to prevent congenital malformations and unnecessary pregnancy terminations, in addition to correcting elevated risk perceptions related to drug use (99). In Norway, a web-based drug information service (www.tryggmammamedisin.no)- similar to a TIS- was established in 2011. The Norwegian DICs are responsible for this service.

1.7. Follow-up of pregnant women by the Norwegian health care system

In Norway, there are national clinical guidelines for antenatal care. Pregnant women should be cared for throughout pregnancy by a general practitioner (GP) and/or a midwife. A basic programme of eight check-ups is recommended, including an ultrasound examination between the 17th and 19th week of pregnancy. A health record card, which has a section for noting chronic diseases and/or current use of medicines, is filled out at each check-up by the GP or midwife (127).

The Norwegian guidelines for obstetric aid recommend that women with chronic diseases such as epilepsy, diabetes and rheumatic diseases are offered expanded follow-up. For example, women with epilepsy (WWE) receive preconception counselling and regular counselling during pregnancy at the Neurology Clinic, ultrasound examination at 11-14 weeks' gestation and expanded ultrasound examination at 18 weeks' gestation, in addition to individually planned obstetric follow-up (128).

1.8. Motivation for the studies and the author's preconceptions

The work included in this thesis is based on my experience from working in a Norwegian DIC. RELIS is a national network of four regional DICs in Norway, answering problem-oriented drug-related questions from health care providers (129). Approximately 13% of the questions to RELIS concern the use of drugs in pregnancy. When including questions regarding breast-feeding, these topics constitute 19% of all queries, as described in Figure IV. Importantly, 86% of the queries received by RELIS are patient-specific (130).

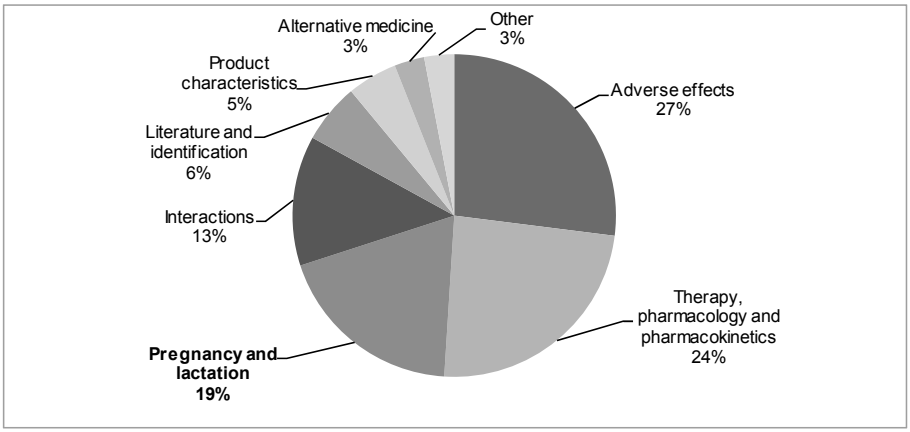

Figure IV. Categories of questions received by RELIS in 2012, n=2586.

As previously described, RELIS launched a web-based drug information service (www.tryggmammamedisin.no) for pregnant and breast-feeding women in 2011. I have been involved in this project since its conception and I am currently the project leader. Questions regarding treatment of pain, allergic rhinitis, psychiatric conditions and asthma are frequently received at www.tryggmammamedisin.no (131).

Because of the frequent queries to RELIS regarding drug use in pregnancy, I became interested in this particular aspect of drug information. I wanted to know more about how drug information on this topic should be disseminated according to the needs of the information users; physicians and pregnant women.

2. AIM

The main aim of this thesis was to examine pregnant women's and physicians' attitudes to, and needs for, information regarding use of medicines in pregnancy. This was undertaken in four papers with the following aims:

Paper I

To compare two commonly used sources that provide advice to physicians regarding drug use in pregnancy; answers from RELIS, and information in the product monographs in FK. Furthermore, to describe the frequency of drug queries made to RELIS regarding the use of drugs during pregnancy.

Paper II

To examine physicians' evaluations of quality, clinical impact and ranking of RELIS with regard to questions regarding drug use in pregnancy.

Paper III

To examine risk perceptions and needs for medicines information among pregnant WWE.

Paper IV

To examine and compare teratogenic risk perceptions and confidence in use of medicines by pairs of pregnant women and GPs, based on assessments of texts from PILs.

3. MATERIAL AND METHODS

The studies included in this thesis were performed using three different approaches, based on four different study populations. Table V provides an overview of design, data collection and study population of the individual studies. In the following, design of the individual studies will be briefly discussed with methodological considerations.

Table V. Methodological overview of the papers included in the thesis.

Paper	Design	Data collection	Study population
I	Descriptive, comparative study	Categorization of advice regarding pregnancy from RELIS and FK for corresponding drugs	443 drug advice
II	Survey	Questionnaire to physicians who consulted RELIS for information on patient-specific drug use during pregnancy	117 physicians
III	Qualitative study	Individual in-depth interviews with pregnant women with epilepsy using antiepileptic drugs	10 women
IV	Survey	Questionnaire to pregnant women attending ultrasound examination in weeks 17-19 of pregnancy and their GPs	171 women 74 GPs 98 pairs of women and GPs

3.1. The descriptive study (*Paper I*)

3.1.1. Data collection

All questions to RELIS regarding pregnancy received during 2003 and 2005 were included. Advice provided by RELIS was compared to the advice in the product monograph in FK for the respective drug. Comparison of advice was based on categorization to one of four categories:

1. Can be used
2. Risk-benefit assessment
3. Should not be used
4. No available information

Substance name with ATC (Anatomical Therapeutic Chemical) code and the year of introduction of the generic substance in Norway was registered, in addition to the trimester or trimesters in question.

3.1.2. Methodological considerations

A possible bias was that one pharmacist at RELIS categorized most of the advice. However, a pilot test among physicians demonstrated acceptable agreement with the categorizations by the pharmacist (Kappa coefficient 0.67). There was a possibility for overestimation of discrepancies in the material as contraindications in FK are often a reason for seeking advice from RELIS.

3.2. The surveys (*Papers II and IV*)

3.2.1. Recruitment of participants

Paper II: A questionnaire was sent consecutively to physicians who consulted RELIS during a one- year period regarding patient-specific drug use in pregnancy.

Paper IV: A questionnaire was handed out to women attending ultrasound examination between weeks 17 and 19 of pregnancy at the Ultrasound Laboratory at the Department of Gynaecology and Obstetrics at Haukeland University Hospital in Bergen, Norway. In the questionnaire, the woman provided the name of her GP and the GP's clinic and a questionnaire was subsequently sent to the GP. A pilot study was carried out to estimate the number of participants needed in the main study.

3.2.2. Data collection

Paper II: The quality of service provided by RELIS was assessed by a five-point Likert scale for statements regarding: a) satisfaction with the service, b) influence on therapeutic decision by the answer provided, and c) recommendation of RELIS' service to colleagues. Clinical impact of the information provided was assessed by predefined categories. The physicians were also asked to rank RELIS and other commonly used sources in terms of their usefulness in providing drug information during pregnancy.

Paper IV: The questionnaire contained authentic texts relating to pregnancy from the PILs for five medicines and one herbal medicine with different indications for use;

- pivmecillinam (Selexid™) for urinary tract infection
- metoclopramide (Afipran™) for pregnancy-induced nausea during the 1st trimester
- paracetamol (Paracet™) for back pain
- escitalopram (Cipralex™) for depression during the 1st trimester

- valeriana officinalis (Valerina Natt™) herbal medicine for insomnia
- dexchlorpheniramine (Polaramin™) for seasonal allergy

Each text was followed by questions regarding:

- A: teratogenic risk of the medicine described in the text on a scale from 0: never teratogenic to 10: always teratogenic
- B: confidence in taking (pregnant women) or prescribing (GPs) the medicine for the given indication (yes or no)
- C: clarity of the text on a scale from 0: exceptionally clear to 3: exceptionally unclear

We considered the least clinical significant difference between pregnant women and GPs assessing teratogenic risk to be two units on the risk scale from 0 to 10.

3.2.3. Methodological considerations

Paper II: Selection bias is possible since the responders may not have been representative for all physicians. However, a high response rate (76%) may have reduced the risk of this bias. The physicians who responded could have felt more inclined to share positive than negative views, although anonymous responses might have reduced this possible influence. The physicians who contacted RELIS may have been more motivated for change in practice compared to those who do not use RELIS. The clinical impact of the answers from RELIS was self-assessed by the physicians and we have no information as to whether the information was transformed into action.

Paper IV: Assessments of teratogenic risks and confidence in use of medicines were based on hypothetical case descriptions, with conditions or indication as a surrogate for a clinical situation. However, if a situation arises in which medical therapy is needed during pregnancy, differences in risk perception within the pair could be of importance for therapeutic decisions. Selection bias is possible among the pregnant women since the level of education and proportion of women taking folic acid was higher, and the proportion of smokers and users of herbal medicines lower compared

to the general population in Norway. However, this may be explained by recruitment from a University Hospital. The responding physicians may have been those with a special interest in the topic, and selection bias was therefore also possible among physicians. The texts chosen for the questionnaire could have affected the results and the indications (for example depression) may have been assessed instead of the actual texts.

3.3. The qualitative study (*Paper III*)

3.3.1. Recruitment of participants

Pregnant WWE, treated with one or more AEDs, who had undergone routine ultrasound screening at 18 weeks of pregnancy without observation of teratogenic effects, were asked to participate. The women were recruited by a nurse or a neurologist at the Neurology Outpatient Clinic, either at Haukeland University Hospital in Bergen, Norway, or at Oslo University Hospital in Oslo, Norway.

3.3.2. Data collection

All women were interviewed at the Neurology Clinic for approximately one hour. The interviews were initiated with a short questionnaire where the participants were asked to provide information regarding their age, week of gestation, type of seizure, present seizure frequency, number of years since the diagnosis was made, number of previous children, and use of AEDs and other medicines. The interview guide was semi-structured and contained open-ended questions regarding the women's:

- Risk perception: experiences and thoughts on using medicines and risking seizures in pregnancy, in addition to physicians' presentation of teratogenic risks.

- Experiences with and needs for medicines information, including participation in decisions regarding therapeutic drug regimens and relations with the health care system

3.3.3. Methodological considerations

A possible selection bias is that we could not include WWE who theoretically could become pregnant, but who had avoided pregnancy because of poorly controlled epilepsy or disabilities. In addition, women carrying a fetus diagnosed with a teratogenic effect were excluded, due to ethical issues. Performing the interviews earlier in pregnancy might have given different results. However, shorter experience of pregnancy and possibly higher levels of concern prior to ultrasound examination, could have given less consistent findings and less time to reflect over the situation. The participating women took part in the follow-up programme for pregnant WWE offered through Norwegian hospitals and the results may not be valid in other populations.

3.4. Analysis of data

3.4.1. Statistical analysis (*Papers I, II and IV*)

Paper I: We introduced two different terms to describe the data. The term 'all advice' included all categories (1-4), while the term 'grouped advice' was constructed by combining categories 2 and 3 (unsafe and possibly unsafe), preserving category 1 (safe use) and excluding category 4 (no information). Introducing the term 'grouped advice' allowed statistical analysis of the categorized advice using McNemar's test. Kappa (κ) statistics (κ coefficient) were used to calculate observer agreement in a pilot test. P values < 0.01 were accepted as statistically significant.

Paper II: The answers provided by GPs and hospital physicians (HPs) were compared by analysis using a Mann–Whitney U exact test. P values < 0.05 were considered to be statistically significant.

Paper IV: To examine differences between pairs of pregnant women and their GPs, data were analysed with mixed linear model analysis (132) for teratogenic risk scores (question A) and generalized estimating equations (GEE) (133) for confidence in use of medicine (question B) and clarity of the text (question C). Multiple linear and logistic regressions were used to examine influence of personal characteristics on the parameters. To analyse the relationship between scores for teratogenic risk (question A) and non-confidence in use of a medicine (question B), we used simple logistic regression. P values ≤ 0.05 were accepted as statistically significant.

3.4.2. Qualitative analysis (Paper III)

The analysis was performed in accordance with the principles of systematic text condensation (134). According to the aims of the study, all three authors defined the categories for presenting the results as (1) risk perception and (2) experience with and needs for medicines information. Quotes from the women were used to illustrate the results.

3.4.3. Choice of methods for analysis

As described above, data were analysed using different methods in the studies performed. Table VI presents the basis for the choice of methods, in addition to some limitations of the chosen methods for analysis.

Table VI. Overview of the methods for statistical and qualitative analysis included in the papers.

Paper	Method	Description of method and reason for choice of method	Some limitations of the method
I	***McNemar's test***	Suitable for **paired proportions of categorical data,** and categorized advice from two information sources were compared.	Designed for use with large samples. Applies only for comparison of two raters.
	Kappa (κ) statistics	Measures **inter-rater agreement,** and in the pilot study it was used to measure agreement between raters with different professions	The value of kappa depends on the number of categories and the prevalence in each category. The method takes no account of the degree of disagreement (counteracted by using weighted kappa).
II	***Mann-Whitney U exact test***	A **non-parametric comparison of two independent groups,** and answers of physicians with different workplaces were compared.	Limitations of non-parametric methods; Information may be wasted. Difficult to make quantitative statements about the actual difference between groups.
III	***Systematic text condensation***	A descriptive and explorative method for **thematic cross-case analysis of qualitative data**. It was used to explore experiences and needs among patients.	Common limitations with other qualitative methods. The cross-case line of thematic analysis and decontextualization of data may lose the individual context.
IV	***Mixed linear model analysis***	Suitable for outcome variables that have **continuous correlated responses.** It was used for comparing responses on a scale from 0-10 in correlated data, due to physicians being paired with all pregnant patients.	Implementation of statistical programs to perform the analysis. The model requires a great deal of ad hoc understanding of the phenomena under study.
	Generalized estimating equations (GEE)	Suitable for outcome variables that have **dichotomous correlated responses**. It was used for comparing responses of yes/no or ordinal categories from 0 to 3 in correlated data, because physicians were paired with all pregnant patients.	Challenges with model selection due to lack of absolute goodness-of-fit tests to aid comparisons among several plausible models. GEE parameter estimates are sensitive to the presence of outliers, and estimates are not efficient if the correlation structure is mis-specified.
	Multiple linear and logistic regression	Multiple regression can examine **dependence of an outcome variable on several other variables** (in this case: personal characteristics) simultaneously. Linear regression was used for the continuous variable (scale from 0 to 10) and logistic regression for the categorical variables (yes/no or ordinal categories from 0-3).	Significance may occur by chance due to multiple testing. Large sample sizes may result in statistical significance even for small effects. Difficult to distinguish between additive effects, conditional relationships and multiple causal pathways of the included variables.

3.5. Ethics and approvals

Paper III: The study was approved by the Regional Committee for Medical Research Ethics and The Norwegian Social Science Data Services. Informed consent was given by the participants and the work was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Paper IV: The study was submitted to the Regional Committee for Medical Research Ethics, but because the patient data were anonymous, it was concluded that approval was not required.

4. MAIN RESULTS

4.1. Paper I

Advice on drug safety in pregnancy – are there differences between commonly used sources of information?

A total of 443 drug advices were categorized, of which 224 were provided in 2003 and 219 in 2005. For 208 (47%) of the drugs, advice differed between RELIS and FK. Advice from FK were significantly ($p < 0.01$) more restrictive than advice from RELIS. There were no differences in the level of consistency between advice;

- for drugs that were newly introduced or those that had been on the market for a longer time (> 8 years)
- that regarded use of drugs in the first trimester or use in the second or third trimester
- that were provided during 2003 or 2005

182 (41%) of the questions submitted to RELIS regarding drug use in pregnancy concerned drugs acting on the nervous system (ATC- group N), 55 questions (12%), concerned drugs acting on the respiratory system (ATC-group R), and 54 questions (12%) concerned anti-infectives for systemic use (ATC-group J). Furthermore, seven out of ten of the substances most frequently enquired about were drugs acting on the nervous system, of which four were SSRIs with citalopram in first place.

4.2. Paper II

Drug use in pregnancy – physicians' evaluation of quality and clinical impact of drug information centres

Of the 162 questionnaires sent to physicians, 123 (76%) were returned, and 117 were included in the analysis. 43% of the participants worked in general practice, 35% were HPs, 9% worked elsewhere and 14% did not state their practice.

The majority of the participants strongly agreed with all three statements regarding the quality of the service;

- satisfaction with the answer
- importance of the answer provided for the therapeutic decision
- recommendation of RELIS' service to colleagues

92% stated that the answer from RELIS had clinical impact on their therapeutic decision and 9% reported that termination of pregnancy was avoided as a result of the information provided.

RELIS was ranked highest among the stated sources providing information on drug use in pregnancy, followed by product monographs, Norwegian drug and therapeutic formulary, colleagues and other sources. GPs ranked the information provided by RELIS significantly higher than HPs.

4.3 Paper III

Risk perception and medicines information needs in pregnant women with epilepsy – a qualitative study

Ten pregnant WWE, aged 22-39 years in 20-34 weeks' gestation, were interviewed. All participants stated that avoiding seizures by taking AEDs in pregnancy outweighed perceived teratogenic risks and self-reported adherence to AED-therapy was high. However, dose adjustments of AEDs during and after pregnancy caused concerns for teratogenicity or seizures. Factors that reduced concerns regarding teratogenic effects of AEDs included ultrasound examinations, checks of fetal heart rate and movements, previous positive experiences of pregnancy outcome, and preconception counselling regarding AED therapy. The women reported restrictive attitudes towards taking medicines for indications other than epilepsy.

The participating women were satisfied with the amount of medicines information provided, though their needs for medicines information were reduced by long-term use of AEDs and restrictive use of other medicines. The women valued their neurologist as their primary source for medicines information. Most women browsed the Internet for health- and pregnancy- related information in general, although some were sceptical to the quality of information on different websites. PILs were read, but were perceived as difficult to understand. The women were exceptionally satisfied with the follow-up provided by the health care system.

4.4. Paper IV

Teratogenic risk perception and confidence in use of medicines in pairs of pregnant women and general practitioners based on patient information leaflets

A total of 300 questionnaires were handed out to pregnant women. 175 responded (response rate 58%) and 171 were included. Questionnaires were sent to 121 different GPs, of whom two were excluded and 74 responded (62% response rate). Since some of the women had the same GP, a total of 98 pairs of pregnant women and GPs were identified.

Pregnant women had significantly higher perceptions of teratogenic risks and lower confidence in use of medicines compared with GPs. The differences between teratogenic perceptions of texts for escitalopram (mean difference -3.3), valeriana officinalis (mean difference -2.4) and metoclopramide (mean difference -2.1) were clinically significant according to our definition of minimum 2 units difference. For escitalopram, the GP was 9.5 times more likely to have confidence in prescribing the medicine than the pregnant woman's confidence in taking it. In contrast, the corresponding odds ratio for dexchlorpheniramine was 2.8.

Both pregnant women and GPs assessed the teratogenic risks in the texts for escitalopram and valeriana officinalis to be highest among the texts, and confidence in use of these medicines was the lowest. None of the participants had confidence in use of the herbal medicine valeriana officinalis. The texts for dexchlorpheniramine and paracetamol were assessed the least teratogenic and were associated with high confidence in use of the medicine. Among all participants, there were only minor differences in the overall score of clarity of all texts, with the exception of the text for escitalopram, which GPs assessed as less clear than the other texts.

5. DISCUSSION

What are the needs for medicines information regarding pregnancy? Through working in a DIC, I had observed frequent questions from physicians in doubt about therapeutic choices for their pregnant patients. This led me to question whether the available information regarding teratogenic drug risks for physicians and their pregnant patients was sufficient and appropriate, or whether there were other factors that could explain this insecurity. I therefore aimed to explore the needs for medicines information among physicians and pregnant women, based on their experiences, attitudes and risk perceptions. In the following, I will present the basis for the four studies performed, discuss the study results in light of other findings and suggest implications for my research.

5.1. Background for performing the studies included in the thesis

To achieve an understanding of the attitudes of and needs for medicines information in pregnancy, different methodologies (from descriptive to explorative) were applied on different study populations (physicians and pregnant women; healthy and with a chronic disease). I first set out to describe and compare advice in medicines information sources regarding pregnancy that are commonly used by physicians (***Paper I***). One of the sources included in the comparison was RELIS, and on the basis of the findings in the first study, an evaluation of the patient-specific advice regarding pregnancy provided by RELIS was sought (***Paper II***).

Having based the first two studies on the perspective of physicians, I wanted to also examine the attitudes of pregnant women regarding medicines information. By interviewing pregnant women using drugs for a chronic disease (epilepsy), a qualitative understanding of risk perceptions and needs for medicines information was

achieved (***Paper III***). Finally, it was desirable to explore the possible differences between pregnant women and their physicians concerning perceptions of risks on use of medicines during pregnancy, and a survey was performed (***Paper IV***).

5.2. What are the needs for drug information in pregnancy?

Several studies have examined needs and desires for drug information in different patient populations (65, 135-137) and scales have been developed and validated (137-140). One example is the Satisfaction with Information about Medicines Scale (SIMS) which aims to assess if a person has received enough information about topics related to prescribed medicines. Based on SIMS, a high level of satisfaction with medicines information is found to be correlated with a high degree of adherence to treatment (138). This may also confirm the findings in ***Paper III;*** adherence to AEDs and satisfaction with drug information was high.

Information needs may vary not only between individuals, but also for an individual at different times depending on diagnosis, state of disease and current knowledge (135, 136). Patients also differ as to whether or not they proactively seek medicines information (139). Studies indicate that patients who have been treated with drugs for a long period of time have a decreased desire for information (135, 136). This is in line with the findings in ***Paper III***, where the participants with a chronic disease reported reduced needs for medicines information.

Studies have also found that patients who express desire for drug information are less concerned and more empowered after receiving additional information. In contrast, those that are less inclined to seek drug information become less empowered with increased drug information load, possibly due to a belief that drug therapy is better decided by the prescriber (137). This reflects the subjectivity of satisfaction with information (139). In ***Paper III***, need for drug information was reduced when the follow-up provided by the health care system was of high-quality. Thus, the setting in which health information is provided is of importance, as is patients' relationship to and confidence in health care providers.

A Norwegian study has shown that drug use is highest among patients with a low level of education, possibly due to a greater scepticism to use of medicines among persons with a high level of education (141). Furthermore, a low level of education is suggested to be associated with a low level of health literacy (142). Health literacy is defined by the World Health Organization (WHO) as representing "the cognitive and social skills which determine the motivation and ability of individuals to gain access to, understand and use information in ways which promote and maintain good health" (143). This implies that health literacy means more than just reading comprehension and that it can enable patients to take control of their own health. The level of health literacy may therefore be an important determinant for patients' individual needs for drug information.

Health literacy is assessed by use of different tests or scales that are tested for reliability (142). Lack of health literacy may have several consequences such as incorrect use of medicines and lack of knowledge in health decisions (142). Health literacy among pregnant women has recently been studied in a cross-sectional, international study. Women with a low level of health literacy had higher teratogenic risk perceptions, less frequent use of medicines and reduced adherence compared to women with a high level of health literacy (144). This indicates that improving health literacy among pregnant women may impact health behaviour. Furthermore, unpublished results from this study showed that the level of health literacy among pregnant women in Norway is relatively low compared to other Western countries (145). Health literacy was not directly measured in ***Paper IV***. Even though the level of education among the pregnant women was high, health literacy may be a factor that contributes to explaining the differences in risk perception and confidence in use of medicines between pregnant women and GPs.

5.2.1. Risk perceptions and needs for drug information

The findings in ***Papers III and IV*** show that risk perceptions are determinants for confidence in use of medicines, and others suggest that risk perceptions may influence

general health behaviour (64). As described in Section 1.4., factors such as Western societies' increased focus on risks may contribute to pregnant women's restrictive attitude to the use of medicines (73). It could be speculated that since pregnant women are expected to refrain from a range of activities that are considered to be dangerous, such as eating cheese or painting walls, they may feel they should at least refrain from taking any kind of foreign substances such as drugs. Furthermore, people have a tendency to overstate risks that have low probability but are dramatic and may have serious consequences, such as being in a plane crash. In contrast, they tend to underestimate more common risks, for example getting diabetes or hypertension (108). The findings in ***Papers III and IV*** of increased teratogenic risk perceptions could possibly be explained by this phenomenon of small, but dramatic risks being overestimated. As described in Section 1.4., distorted risk perceptions may also be due to the legacy of the thalidomide tragedy. To counteract the overestimation of risks, a greater focus on the positive consequences for the health of mother and child of treating medical conditions during pregnancy could be pursued.

The Beliefs about Medicines Questionnaire (BMQ) is validated for use among patients with a range of chronic illnesses. The BMQ contains scales for necessity and concerns to assess positive and negative attitudes to use of medicines (146). In one study using the BMQ, the necessity-concerns difference scores were strongly correlated to adherence, and patients who reported strong concerns about taking medicines had lower adherence (147). These findings may be used for interpretations of the findings in ***Paper III***; that strong beliefs about the necessity of treatment outweighed concerns for negative effects of AEDs in pregnancy. Furthermore, in ***Paper IV***, low confidence in use of a medicine, for example for escitalopram, may be a reflection of a stronger belief in concerns compared to necessities. Consequently, prescribed medicines are not necessarily taken by pregnant women since personal beliefs about medicines are major determinants of adherence.

High teratogenic risk perceptions among pregnant women, as found in ***Paper IV*** and in previous studies (14, 56-62), may be decreased by risk counselling (58, 148). Provision of medicines information through counselling may therefore be important for realistic teratogenic risk perceptions.

5.2.2. Utilization of drug information sources to meet information needs

Physicians value readily available medicines information that is useful for providing advice in a clinical setting (80, 149). These preferences regarding medicines information sources support the findings of DIC as a valued information source and discussion partner (***Paper II***). The results of ***Paper II*** also indicate that information provided by DICs may have clinical consequences. Recent studies from DICs in Denmark and the UK (89, 90, 150) provide further support to the findings of ***Paper II***. The questions to these DICs did not specifically regard drug use in pregnancy, but in the Danish study, 31% of the queries concerned pregnancy and 90% of the answers resulted in an impact on clinical practice. Furthermore, more than 90% of responders were satisfied with the answer (89). In two studies from the UK, about 80% of the answers from DIC were used to manage a current patient (90, 150) and 99% of the responders reported to be satisfied with the service provided (90).

The results from ***Paper IV*** indicate that phrasing of information texts in PILs can influence teratogenic risk perceptions and confidence in use of medicines. Physicians may therefore increase pregnant patients' confidence in prescribed medicines if they explain information in PILs that is contradictory to their own suggestions concerning drug therapy.

5.2.3. Inconsistencies between information sources

As described in Section 1.6., both pregnant women and physicians have access to a range of information sources regarding teratogenic drug effects. However, misinformation and misconceptions can arise from use of sources that are not updated or that provide incorrect advice. Based on the results from ***Paper I***, inconsistencies between sources of information may be common. Others have found inconsistencies in

patient's medicines information sources regarding use in pregnancy (112) and that this may cause confusion and non-adherence among pregnant women (14).

After the publication of ***Paper I***, a similar study from Croatia was published. In this study, risk assessments by clinical pharmacologists counselling pregnant women were compared to the FDA risk categorization system. Agreement of assessments by the two sources was found in only 28% of cases, as compared to 53% agreement rate in ***Paper I***. The Croatian study also measured pregnancy outcomes, and it was found that clinical pharmacologists' risk assessments were the best predictor for pregnancy outcomes (34). The differences in results between the two studies may be explained by different methodology. Nevertheless, the common findings emphasize the problems of inconsistencies between sources that provide advice regarding drug use in pregnancy.

The differences found in ***Paper I*** and in the Croatian study may to some part be expected, and explained by the different standpoints of product-specific and product-independent sources, as explained in Section 1.6.1.1. However, the clinical consequences of differences in advice are important, as the choice of information source may impact the physician's therapeutic decisions, as well as pregnant women's adherence to therapy.

5.2.4. Antidepressants; special information needs?

Some estimate that as many as 18% of women are depressed during pregnancy, and that up to 13% have an episode of major depression (151). Others suggest that the prevalence of major or minor depressive episodes is about 10% (152). Norwegian studies indicate that about 1% of pregnant women use antidepressants (12, 153). Importantly, antidepressants was the drug group that RELIS received most questions about regarding use in pregnancy (***Paper I***), and other studies have documented frequent questions to TIS regarding antidepressants (154, 155). ***Paper I*** also showed that advice for antidepressants were most discordant when comparing advice from the product monograph in FK and RELIS. Furthermore, in ***Paper IV,*** risk perceptions were highest and confidence in drug use lowest for the antidepressant escitalopram.

Others have also shown that confidence in use of antidepressants during pregnancy and adherence to therapy is not only low (156, 157), but lower than use of gastric drugs and antibiotics during pregnancy. This may be due to pregnant women being more concerned about the teratogenic effects of psychotropic drugs than of somatic drugs (59). Even physicians may have increased concerns for prescribing psychotropic drugs during pregnancy, due to the potential effects on the central nervous system. In addition, health care providers do not have unanimous views regarding treatment of depression during pregnancy. For example, GPs differ in their attitudes as to whether antidepressants should be stopped or continued (83).

The findings in ***Papers I and IV*** indicate that physicians and pregnant women are particularly insecure about use of antidepressants. A reason for this may be difficulties to make benefit/risk assessments on this topic. The benefit of antidepressant therapy is that possible impact of depression on the fetus is avoided. Such impact may result in preterm delivery, neonatal symptoms and postpartum depression - which may adversely affect the interaction between mother and infant. Untreated depression may also increase the risk of self-destructive behaviour and psychosis during pregnancy (152). In spite of the widespread use of antidepressants, and SSRIs in particular, during pregnancy, there are conflicting views on their teratogenic risks. Studies on risks of miscarriages, malformations, persistent pulmonary hypertension and long-term effects on neurodevelopment have shown inconsistent results (83, 158). However, if the risks were to be increased above the baseline risk, absolute risks would still be low. What however is known is that use of SSRIs late in pregnancy is associated with transient neonatal discontinuation symptoms, like many other psychotropic drugs (158). Psychotherapy could be a treatment option, either alone or in combination with antidepressants (152).

To summarize, insecurity regarding therapeutic choices for depression in pregnancy may be caused by the unknown consequences of treating or not treating the individual woman. An increased focus to provide information regarding different aspects of using antidepressants in pregnancy is therefore advisable. Individual factors such as a woman's severity of disease, history of drug use, possible concomitant

diseases and risk of self-destructive behaviour, are important determinants for treatment choice.

5.2.5. How should teratogenic risks be presented?

Medicines information regarding pregnancy inherently conveys teratogenic risks. Both in oral and written medicines information, framing of risk information may be important for how teratogenic risks are perceived. The same data may be interpreted differently by individuals due to different attitudes and risk perceptions, resulting in different behaviour (63). Health literacy, as described in Section 5.2., is important for understanding and interpreting medicines information and teratogenic risks (159). Figure V provides examples of different formats for risk communication, and in the following, some of these are further described.

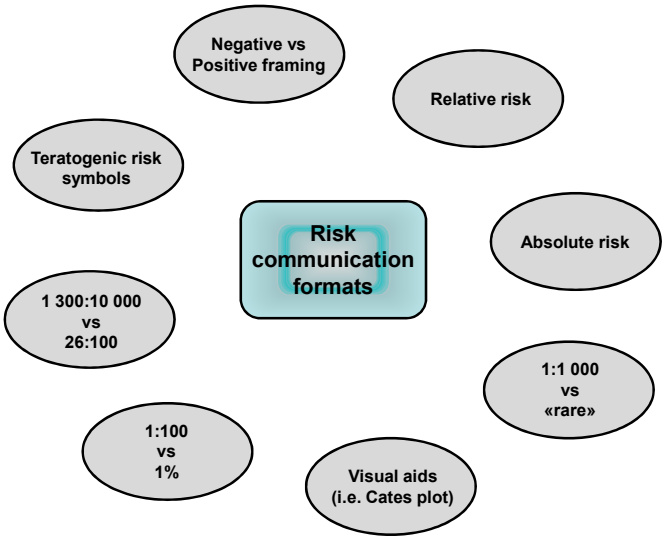

Figure V. Examples of risk communication formats

Negatively-framed risk information (*1-3 % risk of having a child with malformation*) may result in significantly higher risk perceptions among pregnant women compared to positively-framed information (*97-99% chance of having a normal child*) (160).

Relative risks (*a 100% higher risk of having a child with a malformation due to drug exposure*) are intended for comparison of risks in two groups of people, and presenting relative risks to individuals may result in overestimation of risks. Absolute risks or attributable risks are generally perceived as less concerning; (*the normal rate of this malformation is 1/1000 children and this drug may result in twice that rate or 2/1000)* (159). Information in either numeric (1:1000) or mixed numeric/word formats should be preferred to exclusively verbal formats ("rare") since both patients and health care providers may have different understanding of the meaning of verbal descriptors (159, 161). Visual aids for patient's risk assessments have been developed and Figure VI presents an example of such an aid. This matrix may be used to depict the benefits and harm of a treatment (161) and may also be used for communication of teratogenic risks since the baseline risk is included.

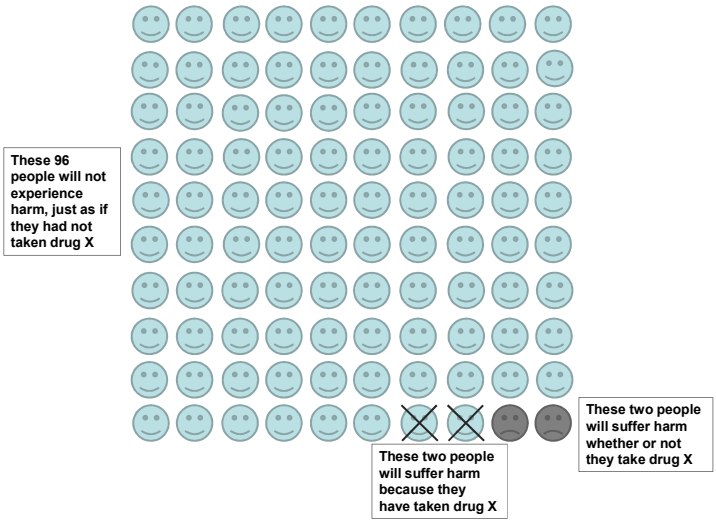

Figure VI. A Cates plot in 100 people showing how drug X doubles the risk of an unspecified harm compared with no treatment. From Cox et al (161).

As the results of both ***Paper IV*** and previous findings (61) have indicated, phrasing and selection of more or less reassuring words and terms can influence risk perceptions and confidence in use of medicines. Based on this, there is potential for framing information in such a way that realistic risks are perceived.

Physicians play a key role in communication and framing of risks to patients and the atmosphere in the patient-physician setting is important for how risk information is perceived (162). Pregnant WWE had great trust in their neurologist as drug information provider and risk communicator (***Paper III***). However, a crucial factor for both patients and physicians is having enough time in the consultation for discussion of benefits and risks of treatment (81, 163).

5.3. Methodological considerations

Limitations of the respective studies are explained in Section 3.1, 3.2., 3.3., and in the respective papers. In the following, I will comment on some methodological considerations of the thesis as a whole.

The studies were performed from the viewpoint of a DIC providing drug advice regarding pregnancy. This has probably influenced the choice of study methods as well as study objectives. Preconceptions of the researchers may have affected interpretation of results, especially for the qualitative study (***Paper III***). Nevertheless, our preconceptions were used to place focus on issues that we had experienced were problematic for physicians and pregnant women.

We chose to use both quantitative (***Papers I, II and IV***) and qualitative methods (***Paper III***). If ***Paper III*** had been omitted, the possibility of exploring life experiences of patients would have been lost, and we consider it enriching for the other studies to include a qualitative perspective.

Generalizability, or internal validity, indicates if the study results are representative for populations other than the one studied. In ***Paper I***, advice from two Norwegian commonly used drug information sources were compared and the results may also be valid in countries where corresponding sources are available. ***Paper II*** was based on queries to DICs (RELIS) from physicians, and the results may be extended to countries where similar services are established. In ***Paper III***, pregnant WWE included in a follow-up programme by the Neurology Clinic at a University Hospital were recruited and the results may therefore not be directly extrapolated to

other populations. In ***Paper IV***, we recruited all women attending ultrasound examination in weeks 17-19 of pregnancy, and their respective GPs. Although the responding women differed from the general population in some of their personal characteristics, this may be expected based on other findings on the types of persons that are inclined to participate in surveys. The results may therefore be valid for pregnant women in general in Norway, and in other countries with similar traditions of drug use in pregnancy.

Health care providers other than physicians were not studied in this thesis. As described in Section 1.6.2.1., midwives and pharmacists are in contact with pregnant women, and a limitation of the thesis is that such health care providers were not included. However, this may be a topic for further research.

The physician's own attitudes, beliefs and expectations may influence the patient's health behaviour. In ***Paper III***, we assessed this interaction indirectly through patient interviews, but including direct measurements of this interaction in ***Papers III and IV*** could have improved the thesis.

5.4. Implications for drug information

Do people need more drug information or do they need the information that already is available to be more clinically useful and understandable? I believe the latter and that the main challenge may be that physicians and pregnant women are unaware of where to find appropriate information, as confirmed by others (81, 82).

A factor that complicates use of medicines information relating to pregnancy is that experts differ in their interpretation of data and opinions regarding teratogenic risks, increasing the risk of differences in advice between information sources. Considering this factor, designing one "golden standard" source - disregarding all other opinions - is not achievable or even desirable.

In Figure VI, I suggest a drug information strategy divided into three levels: individual, group and national. In the following, the suggestions are further explained.

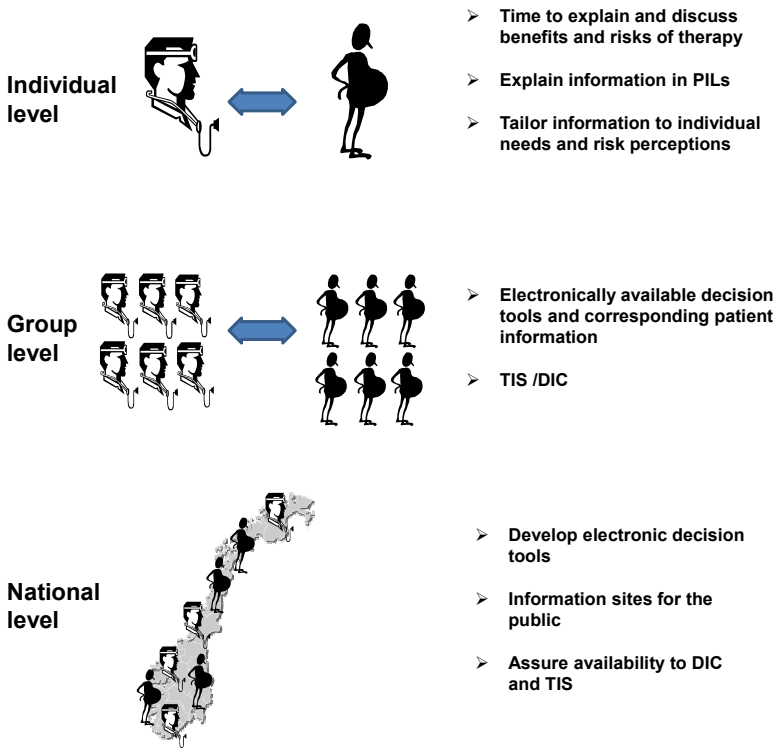

Figure VI. Drug information strategies to physicians and pregnant women.

On the individual level, focus on tailoring medicines information according to the needs and perceptions of each woman could be desirable as this may increase patient satisfaction, empowerment and adherence to drug therapy (135, 139, 164). Individualized counselling does however require sufficient time to discuss treatment choices and to explain medicines information that the patient will read in the PIL. Adequate time for such counselling is especially important in situations where unrealistic risk perceptions are likely to be present or when medicines information sources differ in their advice.

When considering the information needs of physicians as a group, electronic prescription tools providing information on drug use in pregnancy could be utilized, supported by findings that physicians appreciate decision support through electronically available systems (81, 149). Such a tool should be expert-evaluated, such as the Norwegian drug and therapeutic formulary ("Norsk legemiddelhåndbok for

helsepersonell") (165). The electronic system should include information which could be handed to the patient, thus decreasing the risk of inconsistent information. The same system, with corresponding information for prescriber and patient, should also be available online. Considering the increasing technical possibilities of designing online information, I expect that future online medicines information relating to pregnancy could be dynamic and interactive.

Another suggestion is a further focus on patient-specific information provided by DIC and TIS, as this has been shown to be appreciated by both the public and health care providers. DIC and TIS may be particularly important as sources of information and discussion partners for benefit/risk assessment of drug therapy for pregnant women with chronic diseases.

On a national level, availability of appropriate information sources that are independent of the pharmaceutical industry, including DIC, TIS and electronic decision tools, should be assured. There are already governmental Internet- sites established for public information services (166). These sites also contain information for pregnant women, although currently little advice regarding use of medicines (123). Such sites could however be utilized for medicines information systems for both prescribers and patients, as suggested above. In the future, Facebook and Twitter may also be utilized as channels for medicines information relating to pregnancy.

6. CONCLUSIONS

Both pregnant women and physicians need medicines information that can help them make the right therapeutic decisions. The results of the studies included in this thesis indicate that:

- Sources of information differ in advice regarding drug use in pregnancy
- DICs are a valuable source of information for physicians seeking advice for counselling pregnant women
- Pregnant WWE consider the benefits of AED-treatment to outweigh teratogenic risks, but are concerned for dose adjustments
- Pregnant women have higher teratogenic risk perceptions and lower confidence in use of medicines compared to physicians. Phrasing of information texts can influence risk perceptions and confidence in use of medicines.

Consequently, several factors may influence choices of whether or not to prescribe or use medicines in pregnancy:

- Perceived teratogenic risk of medicines
- Phrasing of medicines information and framing of risk information
- Differences in advice between sources of information
- Availability of information sources that are independent of producers of medicines, and that provide patient-specific advice

These factors therefore need to be considered when designing medicines information that aims to meet information needs and impact health behaviour. At the individual level, medicines information should be tailored according to the pregnant woman's risk perception level and desire for information.

7. FUTURE PERSPECTIVES

Based on the results of this thesis, the following research questions are suggested:

- How do variations in wording in patient information texts regarding use of drugs in pregnancy influence pregnant women's risk perceptions?
- How should information regarding use of OTC drugs be provided to pregnant women?
- What kind of medicines information do pharmacists need in order to provide appropriate advice to pregnant women?
- Are needs for medicines information among pregnant women with chronic diseases different to the needs of pregnant women in general?
- What is the impact of medicines information relating to pregnancy provided on governmental Internet- sites?

Several of the suggested studies could benefit from the application of qualitative methods.

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