DEPRESSION DURING PREGNANCY: VIEWS ON ANTIDEPRESSANT USE AND INFORMATION SOURCES OF GENERAL PRACTITIONERS AND PHARMACISTS

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ABSTRACT

Background: The use of antidepressants during pregnancy has increased in recent years. In the Netherlands, almost 2% of all pregnant women are exposed to antidepressants. Although guidelines have been developed on considerations that should be taken into account, prescribing antidepressants during pregnancy is still a subject of debate. In this study, we investigated information sources used by general practitioners (GPs) and pharmacists and their common practices.

Methods: A questionnaire on the use of information sources and the general approach when managing depression during pregnancy was sent out to 1400 health care professionals to assess information sources on drug safety during pregnancy and also the factors that influence decision-making. The questionnaires consisted predominantly of closed multiple-choice questions.

Results: A total of 130 GPs (19%) and 144 pharmacists (21%) responded. The debate appears to be ongoing as to whether or not specialised care for mother and child is indicated in cases of gestational antidepressant use.

Conclusion: Primary health care workers are not univocal concerning therapy for pregnant women with depression. GPs and pharmacists should address the subject during their regular pharmacotherapeutic consensus meetings, preferably in collaboration with the TIS or other professionals in the field.

Key words: depression, pregnancy, antidepressant.

BACKGROUND

Pregnancy is a vulnerable period, also when it comes to the adverse effects of drugs. Antidepressant use is increasing, including among women who plan to become pregnant or are pregnant (1,2). Treatment of depression and anxiety may consist of psychotherapy, medication, electroconvulsive therapy or a combination of several approaches. General practitioners (GPs) treat 86% of the patients with mental health problems themselves, and prescribe drugs in most cases (3).

Doctors are confronted with a novel situation when a patient becomes pregnant, a state in which all nonessential drugs should be avoided. However, pregnancy does not prevent depression, and its prevalence is estimated at between 14% and 20% (4).

Pharmacological treatment during pregnancy requires fine balancing of risks and expected benefits in each individual patient, taking the patients history, presentation and preferences into account. The safety of antidepressant use during pregnancy is still under debate since studies on risks of major malformations, persistent pulmonary

hypertension and long term effects on neurodevelopment report conflicting results (5-8). On the other hand, stress and depression are known to endanger both the mother and pregnancy outcome, including abnormal behavioural development of the infant at follow-up (9). GPs are facing the dilemma of whether or not to prescribe antidepressants. They also have to consider other treatment options such as psychological therapies which have been proven to be effective in mildly to moderately depressed outpatients (10) Because of its relatively low prevalence, it is difficult for each individual GP to gain experience in this specific field. Therefore, it may be difficult for them to deal with this dilemma when they are not able to find useful information or apply the available data in practice (11,12). In the Netherlands 2% of all pregnant women use antidepressants during pregnancy but another 2% stops using them (1). Although fluoxetine is one of the antidepressants with the most published experience and sertraline is considered to have the lowest placental passage, pregnant women use all different kinds of antidepressants, including the ones that have come on to the market only recently (1).

We were interested in reasons for this variety in drug use. The source of information is an important factor that influences GPs' views on managing the mental health problems of pregnant women (13). Inconsistencies between information sources may lead to contradictory views and, as such, may give rise to confusion. For instance, information from pharmaceutical companies is cautious and restricted to the contents of the summary of product characteristics (SPC), which mentions associations between antidepressant use during pregnancy and the risk of pulmonary hypertension, cardiovascular birth defects and neonatal withdrawal syndrome(14,15). The Dutch national Teratology Information Service (TIS), which cites large database studies, reports that although the increased risk of major congenital malformations has to be considered, the absolute risk for individual patients remains small. Poor neonatal adaptation – which is usually mild and transient – may occur. On the other hand, it is not known whether fetal exposure to antidepressants has long-term effects on behaviour and neurodevelopment (9,16). Finally, it is not known whether GPs follow practical guidelines or use local policies.

It was the objective of this study to investigate where GPs and pharmacists in the Netherlands obtain information on the safety of gestational drug use and the pharmacotherapeutic approach when managing depression and anxiety during pregnancy.

METHODS

Context

The University Medical Center (UMC) Utrecht is involved in a research project on the effects of antidepressants during pregnancy. As part of this, we studied treatment policies of the main prescribers of antidepressants, the GPs, and the reactions of pharmacists, who might intervene when a pregnant patient comes to the pharmacy with a prescription for an antidepressant. An inquiry was conducted in a Dutch population of 700 randomly selected GPs and 700 pharmacists. Permission of the ethics committee of the UMC Utrecht was not required to perform the investigation.

Study design

We designed a questionnaire with items addressing policies in general practice in managing of depression and anxiety during pregnancy and the sources of information on this subject. We rated the participants' support for different pharmacotherapeutic approaches by referring to possible treatment options such as stepping down medication or switching to another antidepressant. We also inquired about their views on the first-choice antidepressant during pregnancy and on the question whether special care for the neonate is considered when antidepressants are used until delivery. Answering the 20-item questionnaire would take 15 minutes. The questionnaire and a pre-stamped return envelope were sent out by mail. Randomly selected addresses of eligible GPs were provided by NIVEL (Netherlands Institute for Health Services Research). Pharmacists were extracted randomly from members of the Royal Dutch Pharmaceutical Society (KNMP). The study was conducted in 2006.

We analysed differences in sex and practice characteristics between the two groups of respondents and compared them to the Dutch population of health care workers in the field.

RESULTS

A total of 132 GPs and 144 pharmacists returned the questionnaires, resulting in a response rate of approximately 20%.

Information sources used in pharmacotherapy during pregnancy

Table 1 lists information sources used by GPs and pharmacists in decision-making and in advisory tasks when dealing with pregnant patients. A few participants (among both GPs and pharmacists) use standard works like *Drugs in Pregnancy and Lactation* by Briggs, Freeman and Yaffe (17). Two thirds of GPs and a third of pharmacists never consulted the national TIS, which is a significant difference ($chi^2 = 58.3$; $p < 0.001$). Almost three quarters (72%) of GPs regularly consult pharmacists for information on drugs during pregnancy. Pharmacists, on the other hand, would not consult a specialist such as a psychiatrist, who is a specialist in the field. In the Netherlands, the reference used most frequently by both pharmacists and GPs is the "Pharmacotherapy Compass", the Dutch National Health Insurance System Formulary, issued annually (in Dutch: *Farmacotherapeutisch Kompas*, comparable to the *Physicians' Desk Reference* in the US). The introductory paragraph of each chapter discusses specific drug use during pregnancy. Updates on research as well as information provided by manufacturers are reviewed and followed by recommendations. The majority of the GPs (85%) rely on the information of the *Farmacotherapeutisch Kompas*.

Guidelines issued by the Dutch College of General Practitioners (NHG) – known as NHG standards – are used to a lesser extent.

Views on the therapeutic management of depression and anxiety before and during pregnancy

The results show that GPs' opinions on how to manage depression and anxiety during pregnancy were not univocal. One out of five GPs (21%) said they regularly refer patients to a psychiatrist, while the others sometimes or never do so. Some GPs (9%) state that they sometimes advise terminating the pregnancy when patients who use antidepressants become pregnant, which was also the case for 4% of the pharmacists. Within the professions, opinions on continuing medication, lowering the dose or stepping down varied widely. The majority of the respondents (92% of the GPs and 98% of the pharmacists) never or occasionally advised the patient to substitute the antidepressant drug used for another one. Substituting psychotherapy for medication – in order to prevent drug exposure to the child – was never advised

Table 1. *Information sources used by professionals when applying medication during pregnancy.*

Information sources used by professionals when applying medication during pregnancy									
	General practitioners (N = 128) %				Pharmacists (N = 142) %				Significant difference between GPs and pharmacists?
	Always	Most of the time	Sometimes	Never	Always	Most of the time	Sometimes	Never	
Standard works on drug use in pregnancy and lactation	1	2	5	91	0	3	4	94	ns
National Teratology Information Service	5	11	17	66	16	12	39	33	**
Pharmacist for general practitioners/psychiatrist for pharmacists	5	23	45	28	0	3	27	70	ns
National Health Insurance System Formulary	48	37	13	3	23	23	38	16	**
NHG-standards*	7	23	38	31	5	8	37	51	**
Manufacturer	0	5	21	74	6	7	63	24	**
Internet e.g. Pubmed or Medline (research reports, issued guidelines)	2	9	34	55	2	8	39	51	Ns

* Guidelines issued by the Dutch College of General Practitioners (NHG)
** $p < 0.01$
ns = not significant
nr = not relevant, item concerns 2 questions, one for each group
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by 55% of GPs and 24% of pharmacists; (chi^2 = 30.2; $p < 0.01$). Advice given to women who intend to become pregnant did not differ from advice given to pregnant women.

Arguments in favour of treating pregnant women with antidepressants

Most participants agreed with the statement that the need to treat maternal complaints with antidepressants outweighs possible drug-associated risks for the child. Only 20% of GPs and 58% of pharmacists were aware of the negative effects of depression and anxiety on a child's development. On the other hand, only 4% of GPs and 35% of pharmacists believed antidepressants are not associated with an increase in the risk of birth defects.

Arguments against treating pregnant women with antidepressants

Only a few participants considered maternal depression and anxiety as such as causing no harm to the child, thus antidepressants could be avoided in pregnancy. Most GPs and pharmacists mention possible negative effects on the child as a reason to avoid antidepressants. For one third of GPs and pharmacists a possible neonatal withdrawal syndrome was the most important reason to avoid antidepressants during pregnancy.

First-choice antidepressant during pregnancy

Nine different compounds were mentioned as the antidepressant of first choice during pregnancy. Paroxetine and fluoxetine were mentioned most frequently by GPs; fluoxetine was the favourite among pharmacists. Almost 20% of the GPs answered "no antidepressant at all" and another 20% stated they had no idea, or that they had no idea because of the absence of guidelines. Their reason for choosing a specific antidepressant was usually based on the first choice of their local pharmacotherapeutic consensus groups. Coming in second, they chose a drug because it had the most evidence of being safe to use during pregnancy. However, a minority of GPs (9%) and 5% of the pharmacists still consider St. John's wort to be a good alternative; one out of four participants saw no harm in using valerian during pregnancy. There were no significant differences between the two groups of professionals.

Is special perinatal care necessary?

A total of 13% of the responding GPs and 7% of the pharmacists did not believe that antidepressant use during pregnancy created a situation in which mother and child needed to receive special or additional perinatal attention (chi^2 = 13.1, $p < 0.01$). Another 36% of the GPs and 38% of the pharmacists did not consider antidepressant use to be an indication for delivery under the care of a gynaecologist.

DISCUSSION

We investigated the opinions of general phycicians and their attitudes towards drug treatment of depression during pregnancy. In medical practice the risks and benefits of each individual patient will be weighed carefully, taking all other aspects such as psycho-social environment in to account. That made it difficult to give general answers to all the questions. Nevertheless, from the answers given we still can draw some conclusions. (13).

Limitations

Response rates in studies inquiring into policies are often disappointingly low, because in general practitioners give priority to direct care rather than to participating in research. The 20% response rate in this survey is in line with this. The professionals who returned the questionnaire might be the ones who are most involved with the subject. But then again, our conclusion that information and guidelines should be made available would hold true to an even greater extent. Part of our questions forced the respondents to choose among universal statements without weighing individual nuances. Nevertheless the answers revealed broadly deviating opinions.

CONCLUSION

The data presented reflect the views of individual GPs and pharmacists on how to provide pregnant women with the best treatment, since few had policies they could refer to. Doctors are then faced with a problem, though, because they do not have easy access to information on the safety and efficacy of antidepressants during pregnancy, which they could use to make an evidence-based decision. The more so, since most research data that can be found on the internet do not cover the entire range of possible short-term and long-term effects nor do they account for additional risk factors such as smoking or alcohol use. Therefore the Teratology Information Center – which

evaluates the latest reports and collaborates on exposure studies – should be consulted more often, also since they have counselling services available for individual cases. Also, pharmacists – who seem to be credited to a great extent as being the ones to turn to when it comes to use of medication during pregnancy – could play an important role by initiating local policy meetings, providing easily accessible and interpretative information and reviewing guidelines. Development and implementation of clear policies will mean that pregnant women will no longer be sent from pillar to post.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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REFERENCES

1. **Ververs FF, Kaasenbrood H, Visser GH, Schobben AF, de Jong-van den Berg L, Egberts AC** – Prevalence and patterns of antidepressant drug use during pregnancy. *Eur J Clin Pharmacol* 2006, **62**(10):863-870.
2. **Bakker MK, Kolling P, Berg PB, de Walle HE, de Jong van den Berg LT** – Increase in use of selective serotonin reuptake inhibitors in pregnancy during the last decade, a population-based cohort study from the Netherlands. *Br J Clin Pharmacol* 2008, **65**(4):600-606.
3. **van Rijswijk E, Borghuis M, van de Lisdonk E, Zitman F, van Weel C** – Treatment of mental health problems in general practice: a survey of psychotropics prescribed and other treatments provided. *Int J Clin Pharmacol Ther* 2007, **45**(1):23-29.
4. **Gavin NI, Gaynes BN, Lohr KN, Meltzer-Brody S, Gartlehner G, Swinson T** – Perinatal depression: a systematic review of prevalence and incidence. *Obstet Gynecol* 2005, **106**(5 Pt 1):1071-1083.
5. **Gentile S, Bellantuono C** – Selective serotonin reuptake inhibitor exposure during early pregnancy and the risk of fetal major malformations: focus on paroxetine. *J Clin Psychiatry* 2009, **70**(3):414-22.
6. **Campagne DM** – Fact: antidepressants and anxiolytics are not safe during pregnancy. *Eur J Obstet Gynecol Reprod Biol* 2007, **135**(2):145-148.
7. **Andrade SE, McPhillips H, Loren D, Raebel MA, Lane K, Livingston J, Boudreau DM, Smith DH, Davis RL, Willy ME, *et al.*** – Antidepressant medication use and risk of persistent pulmonary hypertension of the newborn. *Pharmacoepidemiol Drug Saf* 2009, **18**(3):246-252.
8. **Noorlander CW, Ververs FF, Nikkels PG, van Echteld CJ, Visser GH, Smidt MP** – Modulation of serotonin transporter function during fetal development causes dilated heart cardiomyopathy and lifelong behavioral abnormalities. *PLoS ONE* 2008, **3**(7):e2782.
9. **Gentile S** – SSRIs in pregnancy and lactation: emphasis on neurodevelopmental outcome. *CNS Drugs* 2005, **19**(7):623-633.
10. **Casacalenda N, Perry JC, Looper K** – Remission in major depressive disorder: a comparison of pharmacotherapy, psychotherapy, and control conditions. *Am J Psychiatry* 2002, **159**(8):1354-1360.
11. **Altshuler LL, Cohen L, Szuba MP, Burt VK, Gitlin M, Mintz J** – Pharmacologic management of psychiatric illness during pregnancy: dilemmas and guidelines. *Am J Psychiatry* 1996, **153**(5):592-606.
12. **Hairon N** – NICE guidance on antenatal and postnatal mental health. *Nurs Times* 2007, **103**(13):25-26.
13. **Frost Widnes SK, Schjott J** – Advice on drug safety in pregnancy: are there differences between commonly used sources of information? *Drug Saf* 2008, **31**(9):799-806.
14. **Chambers CD, Hernandez-Diaz S, Van Marter LJ, Werler MM, Louik C, Jones KL, Mitchell AA** – Selective serotonin-reuptake inhibitors and risk of persistent pulmonary hypertension of the newborn. *N Engl J Med* 2006, **354**(6):579-587.
15. **Boucher N, Bairam A, Beaulac-Baillargeon L** – A new look at the neonate's clinical presentation after in utero exposure to antidepressants in late pregnancy. *J Clin Psychopharmacol* 2008, **28**(3):334-339.
16. **Zeskind PS, Stephens LE** – Maternal selective serotonin reuptake inhibitor use during pregnancy and newborn neurobehavior. *Pediatrics* 2004, **113**(2):368-375.
17. **Briggs GG, Feeman RK, Yaffe SJ** – Drugs in pregnancy and lactation. 7th edition. *Philadelphia: Lippincott Williams & Wilkins;* 2005.
18. **Gardarsdottir H, Heerdink ER, van Dijk L, Egberts AC** – Indications for antidepressant drug prescribing in general practice in the Netherlands. *J Affect Disord* 2007, **98**(1–2):109-115.
19. **Xu YM, McLaughlin SP, Gunatilaka AA** – Sorbifolivaltrates A-D, diene valepotriates from Valeriana sorbifolia(1). *J Nat Prod* 2007, **70**(12):2045-2048
20. **van Der Hulst LA, van Teijlingen ER, Bonsel GJ, Eskes M, Bleker OP** – Does a pregnant woman's intended place of birth influence her attitudes toward and occurrence of obstetric interventions? *Birth* 2004, **31**(1):28-33