Clinical overview

Use of psychotropic drugs during pregnancy and breast-feeding


Objective: To write clinical guidelines for the use of psychotropic drugs during pregnancy and breast-feeding for daily practice in psychiatry, obstetrics and paediatrics.

Method: As we wanted a guideline with a high degree of consensus among health professionals treating pregnant women with a psychiatric disease, we asked the Danish Psychiatric Society, the Danish Society of Obstetrics and Gynecology, the Danish Paediatric Society and the Danish Society of Clinical Pharmacology to appoint members for the working group. A comprehensive review of the literature was hereafter conducted.

Results: Sertraline and citalopram are first-line treatment among selective serotonin reuptake inhibitor for depression. It is recommended to use lithium for bipolar disorders if an overall assessment finds an indication for mood-stabilizing treatment during pregnancy. Lamotrigine can be used. Valproate and carbamazepin are contraindicated. Olanzapine, risperidone, quetiapine and clozapine can be used for bipolar disorders and schizophrenia.

Conclusion: It is important that health professionals treating fertile women with a psychiatric disease discuss whether psychotropic drugs are needed during pregnancy and how it has to be administered.

Clinical recommendations

- Fertile women with a psychiatric disease should be advised before pregnancy whether psychotropic drugs are needed during pregnancy.
- Valproate and carbamazepine should be avoided if possible for fertile women.
- If antipsychotics are needed, olanzapine is primarily recommended based on the amount of safety data, but risperidone, quetiapine and clozapine can be used.

Additional comments

- This is a literature review. More clinical studies are needed for risk estimation of the different psychotropic drugs with long-term follow-up of the children.

Introduction

Drugs and pregnancy: general observations

Since the thalidomide scandal, the use of drugs during pregnancy has been a sensitive and often controversial topic among patients, politicians, journalists and health professionals. This has been reinforced in recent years along with the growth of the internet and the development of our scientific methods, resulting in a rapid stream of scientific
articles in the area. Particularly, the use of psychotropic drugs during pregnancy seems to attract attention. For instance, in 2011, almost 100 new scientific articles on the use of selective serotonin reuptake inhibitors (SSRIs) during pregnancy were published. These turned out to have far from always consistent results. The communication of such results to the individual patient/patient population will very often rest on personal conviction and philosophy of life with regard to empathy and risk perception. For the media, it is quite easy to find unfortunate events and put them in relation to an apparent inconsistency between professional information sources and scientific messages.

Consumption of psychotropic drugs during pregnancy

The best Danish data show that between 4 and 9% of all pregnant women fill at least one prescription for an antidepressant during pregnancy (Sundhedsstyrelsen www.dkma.dk 2013). A Danish register-based study of more than 800 000 pregnant women in the period from 1997 to 2009 showed that 4183 (0.5%) pregnant women were treated with a SSRI during pregnancy, while 806 (0.1%) discontinued at least 3 months prior (1). There are insufficient data for other psychotropic drugs. The total use of prescription-only medicine during pregnancy is widespread. A Danish population study concerning North Denmark Region showed that the share of first-time pregnant women filling at least one prescription during pregnancy increased from 55% to 61% over a 9-year period from 1999 to 2009 (2).

The perception of teratogenic potential

Congenital abnormalities are common among all newborns. If everything is included, from small and harmless abnormalities such as webbing of fingers or toes (syndactyly) to severe and life-threatening abnormalities with abnormal development of the brain (anencephaly), the incident is approx. 3–4%. Therefore, the possibility of a coincidence between malformation and medication is present, thus without the causality being proven.

The risk of abortions and malformations

The background frequency of congenital malformations and other unwanted pregnancy outcomes, such as miscarriage, premature delivery, low birth weight, neonatal failure to thrive and possible impact on the child's later development, is not always well defined. For practical aspects, it may, however, be assumed that the frequency of congenital malformations in the population, as mentioned, is about 3–4% (3, 4), and that the incidence of miscarriages in Denmark in women, who know that they are pregnant, is around 15–20% (5). However, more recent numbers with a more stringent definition of severe malformations reduce the background frequency to around 2.5%, according to statements from the European Surveillance of Congenital Abnormalities, EUROCAT (http://www.eurocat-network.eu). But this estimate represents a certain under-reporting. The actual frequency of drug-induced congenital malformations is unknown. Schardein has attempted to estimate the risk and finds that less than 1% of all congenital malformations are caused by medicine (3).

The risk of not treating a psychiatric disorder during pregnancy

About 10–15% of all pregnant women experience a depression during pregnancy. The risk of depression seems to be greatest in the last two-thirds (second and third trimester) of the pregnancy. Women previously known with depressive disorder have an increased risk of depression in connection with pregnancy. Pregnancy appears to increase the risk of anxiety, as 10–30% of pregnant women experience such symptoms. In one-third of the persons diagnosed with obsessive-compulsive disorder (OCD), the condition worsens during pregnancy and immediately thereafter, just like the prevalence of depressive disorder is higher. Some studies find that approximately 35% of pregnant women with a bipolar disorder experience relapse despite medical treatment, whereas 85% experience relapse without drugs, primarily in the shape of depressive episodes or mixed episodes with both manic and depressive symptoms at the same time.

Aims of the study

As we wanted a guideline with a high degree of consensus among health professionals treating pregnant women with a psychiatric disease, we asked the Danish Psychiatric Society, the Danish Society of Obstetrics and Gynaecology, the Danish Paediatric Society and the Danish Society of Clinical Pharmacology to appoint members for the working group. A comprehensive review of the literature was hereafter conducted.

Material and methods

The amount of available knowledge about the adverse effects of the individual drugs during pregnancy varies greatly depending on the drug's indi-
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Risk assessment on the basis of available data

How many first trimester exposed without detectable signal do we require before we consider a drug to be safe? Consensus does not exist in scientific societies or from regulatory authorities as to which level of certainty is acceptable. Using historical data for the background frequency (applied value: 3.5%) of congenital abnormalities, it is possible to roughly estimate the following (7, 10):

i) 200 exposed in the first trimester without signs of excess incidence of malformations provide a good certainty (80% power and 5% level of significance) that the real risk is not more than three times higher than the background risk;

ii) 700 exposed in the first trimester without signs of excess incidence of malformations provide a good certainty (80% power and 5% level of significance) that the real risk is not more than two times higher than the background risk;

iii) 2000 exposed in the first trimester without signs of excess incidence of malformations provide a good certainty (80% power and 5% level of significance) that the real risk is not more than 1.5 times higher than the background risk.

If certainty for an even lower risk is demanded, it will require data for many thousand first trimester-exposed pregnant women. Such data are, however, only available for very few medical products. FDA’s classification system, which is under a fundamental restructuring (11), has operated with a very conservative algorithm for the classification of drugs for use during pregnancy. This has led to a very low practical applicability of the formal regulatory classification, as only around 30 medical products have achieved the classification ‘can be used during pregnancy’ (12).

The above estimates apply to the general risk; for specific rare malformations, considerably more cohort data are needed, and these kinds of specific malformations are therefore typically described in case–control studies. Neonatal complications and long-term effects are not included in the above considerations. One example is that in the 1940s, diethylstilbestrol exposure \textit{in utero} was found to lead to an increased risk of uterine cancer, when the child had become an adult (13).

Classification strategy

In this document, the decision as to whether a drug may be used during pregnancy without significantly increased risk of malformations is primarily based on the criteria in EMAS’s guideline. These recommendations, which are discussed in detail above, mean in general the following:

i) As a rule, the guideline demands data on at least 1000 pregnant women without signs of excess incidence of congenital malformations to recommend a drug during pregnancy.

ii) In the cases where this data volume is not available, the recommendations are basically arranged according to the available amount of data.

iii) There may be \textit{justified} deviation from the above.

The risk of other unwanted foetal impacts is discussed on an \textit{ad hoc} basis. Data are primarily obtained from peer-reviewed publications, but in some cases supplemented with unpublished, but well-documented available exposure data from the Swedish Birth Register \url{www.janusinfo.se}.

Drugs and breast-feeding: general observations

All drugs under approx. 1000 kDa transfer into the breast milk. In modern mother-and-child
medicine, risk assessment in connection with breast-feeding is primarily based on a quantitative estimate: how much medication is transferred to the child during breast-feeding? In the overall assessment, however, importance is also attached to available information about possible/probable side-effects in nursed children.

The quantitative estimate can be expressed as a relative infant dose (RID). This is calculated on the basis of measurements of drug concentrations in breast milk, preferably at different maternal doses of the given drug. Based on the highest concentration, the child’s exposure is now estimated as a weight-adjusted percentage of the mother’s exposure. In these estimates, the child is assumed to consume 150 ml breast milk per kg per day. Regarding nortriptyline, which has a relative weight-adjusted dose of 1%, it is possible to calculate the following:

i) dose of the mother: 100 mg/70 kg = 1.4 mg/kg;
ii) exposure of the child: 1% of 1.4 mg/kg = 0.014 mg/kg;
iii) thus, a 5-kg child will be transferred a total of 0.07 mg nortriptyline per day through the breast milk.

Milk–plasma ratio is unfit to contribute with meaningful risk assessment and is an obsolete parameter. In contrast to use during pregnancy, there are no regulatory guidelines indicating criteria for an acceptable exposure of nursed children. Internationally, no formal consensus exists either. As a point of departure, a RID below 10% is considered compatible with breast-feeding. Most drugs have a RID below 1% (14). The decision algorithm is modified in practice by observation of probable side-effects; drugs with undesirable properties regardless of RID (antineoplastic drugs; immune-modulating drugs); or drugs with a very long half-life (risk of accumulation). Finally, it must be added that regardless of RID, a possible hypersensitivity in the child towards a given drug can of course contraindicate the use of it.

Specifically in relation to patients with mental illness

It is a fundamental consideration that exposure during breast-feeding can be avoided by not breast-feeding. As a rule, breast-feeding should in general be established, but in relation to this patient population, circumstances in clinical practice can speak against breast-feeding, even though no risk is estimated to be connected with the child being exposed to the drug via the breast milk in accordance with the following section. For severely depressed or psychotic patients, breast-feeding can thus in practice be impossible or even dangerous for the child.

Disturbed sleep increases the risk of relapse in many psychiatric disorders. Therefore, it is important that mothers with a mental disorder are ensured a good circadian rhythm and a good night’s sleep. This speaks in favour of discontinuing breast-feeding and of formula feeding the child.

As a rule, this guideline uses data from Medications and Mothers’ Milk 2012 (14) for the purpose of quantitative estimates. In certain cases, data may be supplemented with data from peer-reviewed publications. As a rule, this guideline only recommends breast-feeding when RID is below 5%, and any deviations from this are specifically substantiated.

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Results

Non-pharmacological intervention

Specific information about the mental condition can help break the isolation and anxiety often felt by the affected individuals. If suspecting symptoms in the mother, an assessment by her own medical doctor or treatment offer in the municipality should take place. If depression, severe anxiety, OCD or psychotic state is suspected, referral is given to psychiatric evaluation and treatment. Depending on the severity, the treatment takes place either in a private practice or at the hospital. Obstetric wards have established ‘vulnerability teams’ to help in this situation across Denmark.

When the treatment is initiated, it should first be assessed if talk therapy can help. Talk therapy may be the best solution for some conditions to eliminate or reduce the symptoms and to improve family life and the relationship to the unborn child. If there is no improvement or prospects of improvement with talk therapy, medical treatment must be introduced. By medical treatment, both supporting conversations and information are important parts of the total treatment.

Cognitive and interpersonal therapy has a certain effect on depression. Cognitive therapy can also be used to treat anxiety and OCD.

Pharmacological intervention

Depression. About 20% of the Danish population will develop a depression at some point in their lives. The depressive phase can be divided into
varying degrees of severity: mild, moderate and severe depression where the development can happen acutely in a couple of days or come slowly during months.

In a mild depression, the person is marked by sadness and fatigue. Sleep disorders may be present in a mild degree, and the interest in, for example, hobbies, studies or work can be slightly reduced. At this stage, most people are still able to maintain some study activity or do a job.

In moderate depressions, the low spirits, the fatigue, the sleep disorders and the loss of interests are more pronounced. The ability to concentrate will be reduced, and the desire to go to work or to school will disappear. Some people choose to isolate themselves at home, because they cannot cope with going out and be among other people, but also because they lack energy. Things that are used to make them happy no longer have the same effect. The depressed person often has thoughts about death and accidents, some have thoughts about suicide and are tormented by self-recrimination and guilt. Typically, they have a pronounced feeling of despair and lack of self-esteem. Likewise, the sexual desire can also be reduced. The individual can have a tendency to cry a lot, but can also be tormented by irritability, anger and anxiety. The appetite may be reduced, but the opposite – eating for comfort – is also seen.

In the severe depressions, the depressed person is unable to take care of himself and must often be assisted in even the most basic tasks. Some are paralysed to the extent that even facial expressions disappear and they may stop eating and drinking. Severe memory problems and poor concentration are observed. In some cases, delusions and hallucinations emerge, and some persons feel such a pronounced despair that they will attempt to commit suicide.

The risk of not treating depression in pregnant women. Historically, a pregnancy, which by most people is considered to be a happy circumstance, is believed to protect against mental illness. However, this cannot be substantiated. On the contrary, it is now generally accepted that pregnant women have a greater risk of having a depression than non-pregnant women. About 10–15% of all pregnant women experience a depression during pregnancy. The risk of depression seems to be greatest in the last two-thirds (second and third trimester) of the pregnancy. About half of these conditions will continue after the birth of the child (15).

Women previously known with depressive disorder have an increased risk of depression in connection with pregnancy and in the period immediately after the birth of the child. The use of prophylactic treatment with antidepressants during pregnancy has shown to reduce the risk of relapse from about 70% without prophylactic medical treatment to approximately 25% with prophylactic medical treatment (16). Psycho-social and biological factors in connection with the pregnancy probably play a role in the emergence of the depression, but clinically, the depressive symptoms do not differ significantly from the symptoms of non-pregnant women.

Depression in pregnant women does not only pose a direct risk to the woman, but also to the unborn child. Untreated depression in pregnant women has been linked to an increased risk of abnormal bleeding during pregnancy, miscarriage, premature birth, foetal death, pre-eclampsia and other birth complications as well as the child’s failure to thrive after the birth and decreased breastfeeding initiation (17).

For the woman, the illness can result in poor nutritional condition, increased alcohol and tobacco consumption, other unhealthy habits of life, suicide-related behaviour and regular suicide attempts (18–20) as well as a poor utilization of the offers of the pregnancy care. All these factors can cause harm to her unborn child. Suicide among pregnant women is rare, but a British study showed that of all the women who died during pregnancy, 28% committed suicide (21). Also abnormal biological factors (e.g. increased concentration of adrenocortical hormone), which are seen in at least half of the depressed patients, are suspected to be harmful to the foetus, partly by affecting the brain development in the foetus in a negative way, partly by the fact that the foetus will later be hypersensitive to stress factors. Thus, an increased prevalence of depression is shown in 18-year-old children of mothers who were not treated during pregnancy for their depression (22). In children exposed to antidepressants during pregnancy, no signs of behavioural or emotional problems were detected when assessed at the age of 4–5 years. Untreated depression during pregnancy appears to increase the risk of behavioural problems in the child (23). Finally, a depression which continues after the birth will affect the mother’s ability to take care of her child.

Medical treatment of women of child-bearing age with depression. It is important that medical doctors, midwives and other healthcare professionals are aware of any depressive symptoms in pregnant women. This applies in particularly to women with a previous depression. According to the guidelines in the field of the Danish Health and Medicines

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Authority, the possibilities of psychotherapeutic treatment should always be considered in depression in pregnant women (24). Medical antidepressive treatment can in some cases be necessary and justified, for instance in case of a severe depression or in case of high risk of recurrence of the depression if an already initiated medical treatment is discontinued. According to the Danish Health and Medicines Authority’s guidelines, the treatment should take place in consultation with a specialist in psychiatry. The potential benefits and the harmful effects must be balanced against the risk an insufficiently treated depression poses to the woman and her unborn child. Moreover, the treatment of pregnant women with antidepressants should in Denmark observe the guidelines in the field of the Danish Health and Medicines Authority.

Anxiety and OCD. About 10–15% of the Danish population will have a severe anxiety disorder during their lives. These disorders are more frequent in women than in men and are divided into a number of different types. Social phobia is characterized by severe nervousness and anxiety if the person must be together with others. Others experience anxiety in specific situations, for example when they have to sit for an exam or speak in front of a group. Some people will experience panic disorder, where the anxiety is completely unexpected and in short-term attacks. Others suffer from agoraphobia, which is characterized by fear to leave home, to take the bus, to take the train, to be in crowds or to be alone at home. Even others suffer from generalized anxiety disorder with constant nervousness and worry.

Obsessive-compulsive disorder is an anxiety disorder which may consist of obsessive thoughts and/or patterns of compulsive behaviour and which may vary a lot in terms of both the symptomatology and how much it affects everyday life. Doubt and uncertainty are key parts of the disorder and can be seriously disabling.

Obsessions are often dramatic, unpleasant thoughts occurring over and over, causing anxiety, stress and perhaps feelings of guilt and self-recrimination. Compulsions may consist of washing rituals, compulsion to check, rituals of counting and visualizing (mental compulsive behaviour), and that you need to think positive (mental obsessive thoughts), to manage and organize things in certain ways, symmetry and superstitious rituals.

The risk of not treating anxiety and OCD in pregnant women. Pregnancy appears to increase the risk of anxiety, as 10–30% of pregnant women experience such symptoms. Approximately 4% of pregnant women without previous OCD show signs of OCD 6 weeks after the birth (25). In one-third of the persons diagnosed with OCD, the condition worsens during pregnancy and immediately thereafter, just like the prevalence of depressive disorder is higher (26). Persons diagnosed with OCD appear to have a prolonged birth and several obstetric complications (27) as the woman can be so tormented by anxiety or OCD that she is unable to give birth vaginally. After the birth, OCD can be seen in, for example, the mother refraining from bathing or taking care of the child, because she is abnormally afraid to harm it. Violent fantasies aimed at the child may appear leading to a tormented and concerned mother fearing she will act on these fantasies. This is in contrast to the psychotic person who does not worry about this. Both anxiety and OCD can be treated with good results with evidence-based psychotherapy. In a few cases, the treatment with an antidepressant may be indicated. In very rare cases, combination with an antipsychotic drug may be indicated.

Treatment with SSRI antidepressants

Recommendations. Planned pregnancy and start-up during pregnancy.

i) Prescription and control of the patient’s treatment should ideally be performed in collaboration with a specialist in psychiatry.

ii) Sertraline and citalopram are first-line treatment among SSRI. The advantage of sertraline is that the treatment apparently can be continued during breast-feeding without problems.

iii) Fluoxetine is not first-line treatment despite the highest amount of data, among other things because of casuistic reports on neonatal death, and because the drug is released slowly in the body of the newborns.

iv) Paroxetine may be associated with an increased prevalence of malformations as well as neonatal complications and is therefore not recommended.

v) Escitalopram is not found to constitute any problems during pregnancy.

vi) Fluvoxamine is not recommended due to limited or no data.

Pregnancy occurring during an existing treatment with SSRI

i) Ideally, the patient should be assessed by a specialist in psychiatry.

ii) In case of pregnancy during an existing treatment with fluoxetine, change is only
recommended if it is considered to be safe in relation to the patient’s disease.

iii) Regarding treatment with escitalopram, the treatment can be continued during pregnancy.

iv) Regarding treatment with fluvoxamine, change to another treatment is recommended, but only if it is considered to be safe in relation to the patient’s disease.

v) Paroxetine treatment should only continue under extraordinary strict indication.

Birth. In treatment with SSRI up to birth, there is a risk of neonatal complications. These need normally no treatment. Studies have shown an increased risk of persistent pulmonary hypertension, which, however, occurs very rarely. Overall, outpatient birth is not recommended, and the parents should receive information about typical symptoms in the child, so that the child can be observed and the right treatment initiated. Discontinuation of SSRI is not recommended, if the treatment is still indicated.

Breast-feeding.

i) It is important to be discussed with the pregnant women whether she wants to breast-feed. In some cases, formula feeding is a good alternative.

ii) If breast-feeding is wanted, sertraline and paroxetine are recommended, as these two drugs have the fewest reported side-effects and the smallest transfer into the breast milk.

iii) There are casuistic reports of accumulation of fluoxetine in nursed children, and most reports on symptoms by use of fluoxetine and citalopram, which are therefore not recommended. However, in connection with treatment during pregnancy, the treatment can continue during breast-feeding provided that information about possible side-effects in the child is given. In particular, one must pay attention to lack of wellbeing, and whether the child achieves the expected weight gain. In cases of doubt, the drug can be measured in the child’s blood.

iv) Escitalopram and fluvoxamine are not recommended due to limited or no data.

Advice for pregnant woman not already in treatment. When advising a pregnant woman about antidepressive treatment of depression, the decision is simple in case of mild as well as severe illness: mild cases should not be treated with drugs (24), and in severe cases, medical antidepressive treatment is inevitable. It is the middle group which causes problems and where non-pharmacological treatments of course should be considered first, namely the possibility of evidence-based psychotherapeutic treatment, that is with interpersonal therapy or cognitive therapy. If this is not sufficient or possible, the above points should be discussed thoroughly with the woman, so she can make her choice on the best basis possible. In particular, it is important to inform about the risk of congenital abnormalities in all circumstances, also without the use of medical treatment. So if the woman chooses to take drugs and later gives birth to a child with a birth defect, it does not have to be due to her choice, but may have occurred anyway.

From everything we know, the problem is particularly heart malformations, but number needed to treat, one to harm is high. Paroxetine and perhaps also fluoxetine are considered to be the most risky. Newer drugs should be avoided as we have at least knowledge about those. With regard to fluoxetine, it should be remembered that it should not be taken by breast-feeding women due to the risk of accumulation in the child.

If the woman has previously had an effect of a particular drug and nothing in particular speaks against this substance, it should be used. The risk of neonatal complications should be mentioned, so that the woman is prepared for them, and in particular, the increased risk of persistent pulmonary hypertension (PPHN) should be mentioned, because this complication, although rarely, may be fatal.

Advice for woman who is in medical treatment, and who wants to be pregnant. In good time, it should be considered with the woman if there should be an attempt to phase out the treatment. These considerations should, among other things, contain an estimate of the risk of recurrence, how severe the depression was when it was worst and whether the woman was suicidal. If the woman has previously tried to phase out her treatment and it lead to recurrence, it may speak against trying to phase out. Also, residual symptoms in spite of treatment predict recurrence of the depression when phasing out.

If you choose to phase out, the woman should be offered careful follow-up to provide quick assistance in the event of recurrence. If the woman is treated with paroxetine, and phasing out is contraindicated, she should be switched to another SSRI as an attempt, in accordance with the above. Some women are treated with several different psychotropic drugs at the same time, for example an antidepressant and an antipsychotic as a sedative. Such treatment should as far as possible be simplified to include only one single SSRI [or possibly

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one single tricyclic antidepressant (TCA)], because it is not possible to predict how several different substances will interact in the growing foetus.

A routine phasing out of SSRI 2 weeks prior to the birth to avoid neonatal complications is not recommended (28, 29).

Advice to woman already in treatment, who discovers she is pregnant. The decision about what to do depends on for how long the woman has been pregnant when she discovers that she is pregnant. Often, she will be well through the first trimester, and the risk of severe malformations must be assumed to be over. Therefore, there will be no reason to stop the treatment. However, the risk of PPHN still persists. Therefore, some authors recommend that the drug which the woman is already treated with is continued to not risk recurrence if the treatment is changed.

Background

The effect of selective serotonin reuptake inhibitors (SSRI) for the treatment of depression, OCD and anxiety is scientifically well documented. Cognitive therapy and interpersonal psychotherapy are also well documented in non-pregnant women, and a few studies have shown they are effective in pregnant women too. Therefore, these types of therapies are in principle preferred in mild to moderate depression and in anxiety disorders in pregnant women instead of medical treatment. One of the problems, however, is that they are often not easily accessible, among other things, due to a lack of qualified therapists. In addition to this, not all respond to psychotherapy. In many studies, the success rate in non-pregnant women is around 60%. It also often happens that women already in antidepressive treatment want to become pregnant. Or that the woman who is treated with SSRI discovers that she is a few weeks to months into her pregnancy. The general practitioner, obstetricians and psychiatrists will therefore often have to advise pregnant women about such a treatment.

What risks are present?

It is well known that the incidence of miscarriages and stillbirths can be influenced by, for example, medication intake during pregnancy, even though it normally occurs very rarely. There may be neonatal complications, and a relatively new area is the so-called behavioural teratology, that is whether the child’s motor, intellectual and emotional development can be influenced by drugs given during pregnancy.

On the other hand, a number of studies indicate that untreated depression in itself may harm the unborn child. However, none of the SSRI drugs are categorically recommended for the treatment of depression during pregnancy. All of these drugs should only be used if the benefits for the pregnant woman (and her unborn child) outweigh the potential side-effects.

Miscarriages and stillbirth

It is estimated that around 20% of all pregnancies end up with a miscarriage, but it is difficult to assess for certain, as many miscarriages are so early that they can be confused with a late coming period. Moreover, the risk depends on the woman’s age and lifestyle. The frequency of miscarriages, where the woman knows that she is pregnant, is about 15–20%. The results concerning the impact of SSRI on the frequency of abortion are not clear (30).

An important study of 937 women who took SSRI during pregnancy, compared with a similar number who did not, showed 13% abortions in the SSRI group against 8% in the control group (31). Other studies suggest something similar (32). The studies are not without methodological problems. For instance, in the first mentioned study, there were more smokers and more women who had previously had miscarriages in the group of women who took SSRI than in the control group.

Possibly, the increased incidence of miscarriage is specifically associated with paroxetine and venlafaxine. To be on the safe side, the woman, when advised about choice of treatment, should be warned about the risk of miscarriage possibly being increased. In two large studies from Norway and Denmark, SSRI during pregnancy was not associated with significantly increased risk of stillbirth or neonatal death (33, 34). A large Danish register study from 2013 with more than 1 million pregnancies found a slightly increased risk of miscarriage by the use of antidepressant drugs during pregnancy, but this risk could not be replicated when age and mental illness were taken into account. Hence, no increased risk was found in using SSRI in pregnant women with depression compared to women with untreated depression (35).

Congenital malformations

There are many statements, the majority of epidemiological nature, which shed light on the risk of congenital malformations in children exposed to SSRI during pregnancy. These are rather heteroge-
neous both in terms of quality and quantity of data as well as definitions of exposure and outcome. Therefore, it is difficult to get an overview of methodological details, multiple stratifications, odds ratios and incomparability between these studies. Thus, here comes a short summary of the largest and best statements:

A very large meta-analysis was published in 2013 (36). More than 50 000 SSRI-exposed pregnant women were included, and no overall increased risk of congenital abnormalities was found, RR 0.93 (CI: 0.85–1.02). In studies with outcome data for cardiovascular malformations including a total of more than 20 000 SSRI-exposed pregnant women, a slightly increased risk was found, RR 1.36 (CI: 1.08–1.71). A significant part of this signal is carried by septal defects, RR 1.40 (CI: 1.10–1.77). Some studies – but not all – have shown a specific increased risk of heart malformations by paroxetine and fluoxetine exposure. In the meta-analysis, a signal specifically for paroxetine, but not for fluoxetine, was found. Even though there is no consensus as to whether this is a real signal, most recommend avoiding these two drugs during pregnancy. However, there may be clinical cases where switching treatment from a current effective treatment with paroxetine or fluoxetine is not rational, because the risk for the mother with a drug change is greater than the hypothetical risk for the foetus.

Some important specific studies (all of which are included in the above meta-analysis) must be mentioned.

Very large Swedish and Finnish studies show that if SSRIs are resulting in malformations, they are located at the heart (37–39). However, this difference is not statistically significant compared to the background population (40). Heart malformations in general were not found more frequently than you would expect, but atrium and ventricular septal defects were more frequent. Among non-medicated women, the risk was 0.5%, whereas it was 0.8% among those taking SSRI. Number needed to treat, one to harm, (NNH) was calculated to 246. This means that more than 246 women must be treated with SSRI to cause one additional case of septal defect. In addition to this, a number of these are asymptomatic. It cannot be ruled out that many septal defects were only found, because the foetuses known to have been exposed to SSRI during pregnancy were examined extra carefully.

In a methodological elegant Danish register study, the frequency of heart malformations of the 4183 children exposed to SSRI was compared with the frequency of children whose mothers had previously been taken SSRI, but who discontinued with the drug prior to pregnancy and resumed treatment after the birth. The risk of heart malformations was increased equally for both groups (1). This suggests confounding by indication or selection bias, which means that the abnormalities were not caused by the SSRI exposure, but by other factors, which are common for the women who took the drug and the women who discontinued the treatment. A large pharmacoepidemiological study from the USA with 65 000 pregnant women who have used antidepressants in the first trimester has found no increased risk of cardiac malformations (41).

Reduced foetal development and premature birth

Some studies, but not all, suggest that the treatment with SSRI during pregnancy can lead to premature birth and that children born at term are smaller. However, it is difficult to estimate as some studies show that untreated depression in itself may result in premature birth and low birth weight. To be on the safe side, however, information about the risk should be provided (42, 43).

Complications in connection with the birth:

Between 15 and 30% of children whose mothers have taken a SSRI in the last time up to the birth will hours to days after birth show symptoms, which possibly are discontinuation symptoms (44). Spasms have also been seen (36). The symptoms cease spontaneously and require generally no treatment, but serious cases requiring treatment, however, occur. The significance of the symptoms is first and foremost that they can be confused with similar symptoms of serious diseases, such as low blood glucose and brain damage, and there may be problems in relation to the establishment of breastfeeding or mother-and-child bonding. Therefore, in some obstetrics wards, the children are observed for about 24 h, before mother and child are discharged. If the symptoms are especially pronounced, you can choose to observe the child in a neonatal ward. A Danish study of children born to SSRI-treated mothers showed lower average Apgar score and a higher degree of hospitalization on neonatal wards for these children compared with control children (45). A Danish register study from 2013 shows that the use of SSRI increases the risk of low Apgar score independent of the mother’s depression (46). In principle, the symptoms can occur in connection with all types of SSRI, but one study has found paroxetine to be particularly frequently associated with these (47).
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The woman should be informed about the risk that the child can have these symptoms, and what she should do in this case. A register study of more than 120,000 newborns from the period 1998 to 2001 showed no effect on the newborn child’s health by reducing exposure to SSRI towards the end of the pregnancy (29).

Persistent pulmonary hypertension (PPHN)

In the minutes after the birth, a number of changes occur in the child’s circulatory system. This process is controlled, among other things, by prostaglandins, and it is expected that serotonin outside the central nervous system also participates. This may be due to the properties of this substance on blood vessels. A number of aspects and diseases can interfere with this important process. Maldevelopment of the lungs, diaphragmatic hernia and meconium aspiration can thus among many diseases and conditions result in PPHN, but studies indicate that the risk is increased if the mother is in treatment with SSRI after the 20th pregnancy week. The symptoms appear immediately after the birth and include dyspnoea and cyanosis. The condition can often be treated, but is serious and potentially life-threatening.

A recent population-based cohort study from the Nordic countries comprised 1.6 million newborn babies born after pregnancy week 33. The frequency of PPHN among non-exposed children was 1.2 per 1000, whereas among children exposed to SSRIs after week 20, it was 3 per 1000. This gives an adjusted odds ratio of 2.1 (95% CI 1.5–3.0). The risk was increased roughly in the same degree for all types of SSRI, which implies that it is a class effect (48). Other small studies have also pointed to an increased risk of this condition. A new meta-analysis of PPHN showed that early exposure to SSRI does not increase the risk, whereas exposure late in the pregnancy (after week 20) increases the risk by a factor 2.50 (95% CI 1.32–4.73), the absolute frequency was 2.9 to 3.5 per 1000 newborns, which lead to NNH being between 286 and 351 (49). The increased risk can probably be eliminated if the mother can do without SSRI in, for example, the last month before the birth. However, the problem is that the risk of relapse is increased just as she is about to give birth.

Brain development and emotional development

In experimental animal models, primarily for rodents, SSRI affects the early brain development. A prospective study of 99 pregnant women who used SSRI and 570 pregnant women with depressive symptoms who took no antidepressive drugs showed that untreated depression was associated with lower rate of growth of the foetus’ body and head, whereas the treated women’s foetuses had less growth rate of the head, but not of the rest of the body. The difference between the head size of the two groups was, however, only 4 mm (50). A small MRI study of 33 children who had been exposed to SSRI suggested that they had an increased incidence of the so-called Chiari malformation type 1, which is caused by herniation of the cerebellar tonsils into the spinal canal and which may be asymptomatic or cause, for example headache. The result is interesting, but must be replicated before therapeutic consequences can be taken (51).

Unfortunately, only few human follow-up data for many types of antidepressants exist, but the existing studies show no correlation between the drug and the brain development of the foetus measured with regard to intelligence development and on a number of emotional and motor parameters. An American study (52) and a Danish (53), however, found associations with slightly delayed motor development. In a follow-up on the Danish study, however, no correlation was found between exposure to antidepressants and behaviour at the age of 4–5 (23). The studies are difficult to interpret due to the many sources of error. For example, the depression in the mother, according to several studies, can in itself delay the child’s development, and this effect cannot be distinguished from the effect of the drug. Such a correlation was found in the before-mentioned Danish study, where maternal depression, probably after the birth, was a predictor for the child’s behavioural problems.

One study should be mentioned to illustrate the problems of assessing such scientific results: Croen et al. (54) studied 298 cases of Asperger’s syndrome (AS) and found that 6.7% of the women who had a child with this syndrome had taken SSRI during pregnancy, whereas only 3.3% of healthy children’s mothers had taken SSRI. This means that the frequency of AS seems to have doubled if the mother took SSRI. Fortunately, the risk of AS is very low: approximately 0.26 per 1000 children. So, even if the risk is doubled, it is still very low. The authors do not rule out that what they show is in fact a genetic predisposition for AS: the women who received treatment had psychological difficulties due to Asperger features, which increased the risk of depression or anxiety and subsequently
SSRI treatment. At the same time, their children had an increased risk of AS, as there is a considerable hereditary element in the disease. Another possibility is that the children’s illness is caused by the mother’s illness and not her treatment, that is that her depression disturbed the development of their connection with other people. In a Danish register study of more than 600 000 children, no link was found between exposure to antidepressant drugs in utero and autism spectrum disorders (55). The problems relating to change of the child’s behaviour during childhood is important to be aware of in future, so that new and more thorough studies can be designed to obtain certain knowledge. Furthermore, it is a major problem in the existing studies that the child is only followed until it was 5–10 years old. However, one study shows that the worser the depressive symptoms the woman had during pregnancy, the greater the risk that her child had had a depression at the age of 18 (22).

Treatment with serotonin norepinephrine reuptake inhibitors

**Recommendations. Planned pregnancy and start-up during pregnancy.** Venlafaxine and duloxetine are not recommended as first-line treatment during pregnancy. For venlafaxine, however, the data volume is extensive and meets the criteria, but cannot match the number of studies of SSRI. The data are insufficient regarding duloxetine.

**Pregnancy occurring during an existing treatment.** Venlafaxine is not recommended as first-line treatment during pregnancy. The same applies to duloxetine. Ongoing clinical satisfactory treatment with venlafaxine should be continued. Ongoing duloxetine treatment should be changed. However, if the woman has not previously responded to other treatment, it calls for a continuation of the ongoing treatment.

**Breast-feeding.** As a rule, venlafaxine is not recommended as RID is around 7–8%, although side-effects have not been described in the nursed child. Duloxetine can be used as RID is around 1%. No side-effects have been described in nursed children.

**Background.** There are only scarce data on the use of these drugs during pregnancy. No studies have been published of possible long-term effects on the child after exposure in foetal life. One prospective comparative study of 150 women using venlafaxine (56) and a case series with 11 women have been published, overall, without signs of teratogenicity (57).

Regarding venlafaxine, Swedish data for more than 1600 first trimester-exposed pregnant women show no increased risk of unwanted foetal impact. Regarding duloxetine, data exist for around 350 first trimester-exposed pregnant women (58–60). There are casuistic reports on problems in newborns, but there are no comparative studies. Swedish statements of women who have used serotonin norepinephrine reuptake inhibitors (SNRI) found that the symptoms in newborns reminded very much about those seen during treatment with an SSRI. This study found no signs of teratogenicity, but rather an increased risk of premature birth (61).

A large pharmacoepidemiological study from the USA with 6900 women exposed to SNRI found no significant increased risk of heart malformations in the child after checking for confounders as physical illness in the mother (41).

Venlafaxine has been detected in the blood of nursed infants without detectable effects on the children. However, only data on a total of 12 exposed children have been published (62).

Treatment with noradrenergic and specific serotonergic antidepressant (NaSSA)

**Recommendations. Planned pregnancy and start-up during pregnancy.** Due to inadequate data, mirtazapine and mianserin are not recommended during pregnancy.

**Pregnancy occurring during an existing treatment.** Mirtazapine and mianserin are not recommended during pregnancy. However, if the woman has not previously responded to other treatment, it calls for a continuation of the ongoing treatment.

**Breast-feeding.** Due to inadequate data, mirtazapine and mianserin are not recommended during breast-feeding.

**Background.** Mirtazapine and mianserin exhibit their antidepressant effect by impacting the monoaminergic system in the brain. There are only scarce data on the use of these drugs during pregnancy. No studies have been published on possible long-term effects on the child after exposure during pregnancy. In a prospective follow-up study of 104 women who took mirtazapine, but where 35% also took another type of antidepressant drug, sedative drugs or mood-stabilizing drug, there were no signs of teratogenicity (63). Increased risk of premature birth on a par with other antidepressive...
drugs and increased risk of miscarriage were found. But this may be a matter of confounding by indication.

Treatment with tricyclic antidepressants

**Recommendations.** In general, tricyclic antidepressants are not recommended as first-line treatment of a depression. The data volume for some TCAs meets the criteria, but significantly more data exist on the use of SSRI in pregnant women and women breast-feeding.

**Planned pregnancy and start-up during pregnancy.** Tricyclic antidepressants (amitriptyline, clomipramine, imipramine and nortriptyline) do not seem to be associated with an increased risk of malformations. The data volume of these drugs meets the criteria stated in the introduction. The other TCAs cannot be recommended due to scarce data.

**Pregnancy occurring during an existing treatment.** Plasma monitoring of TCAs should be carried out continuously during the pregnancy, for example every 3 months, as there may be a risk that the conversion of TCA is changed, so that concentration in the blood becomes higher than intended.

**Birth.** Tricyclic antidepressants are associated with an increased risk of temporary impact on the child just after the birth. The newborn child may present with symptoms in the shape of increased crying, constipation, problems with urinating and nausea.

**Breast-feeding.** RID for amitriptyline, nortriptyline, clomipramine and imipramine is about 1–3%. No serious side-effects are reported in nursed children by maternal treatment with amitriptyline, clomipramine, imipramine and nortriptyline.

**Background.** Tricyclic antidepressants. Some of the substances are chemically related. For example, amitriptyline is metabolized to nortriptyline and similarly, clomipramine and imipramine share the same basic structure. Only scarce or no human data have been published on the use of maprotiline and dosulepin during pregnancy.

Previous studies suggested a possible association between malformations of the extremities and the use of clomipramine, imipramine, nortriptyline or amitriptyline during pregnancy (64). Subsequent studies, including three prospective and a large case series, however, have not been able to confirm the association. The studies are based on about 400 exposed, but with very different study design (65). A Swedish register study of 14 821 women treated with antidepressants finds that clomipramine leads to an increased risk (OR: 1.84) for ventricular septal defect and atrial septal defect (39). But at the same time, it is stated that there may be a confounding by indication, which is why it is recommended to avoid start-up in case of planned pregnancy, whereas there is no reason to continue during a pregnancy. There are no signs of teratogenic effect of doxepin, which, however, is based on scarce and unpublished data from a monitoring programme. Symptoms compatible with a discontinuation reaction in newborns exposed to imipramine or clomipramine are described. No reports of symptoms after exposure to amitriptyline or nortriptyline are published. One case of urinary retention in a newborn child exposed to nortriptyline in utero as well as one case of neonatal paralytic ileus after exposure to doxepin and chlorpromazine in the third trimester is described.

There are a few studies concerning the development of children until preschool age, who during pregnancy have been exposed to TCA (66). Two studies have not been able to demonstrate impact of IQ, language or behavioural development after exposure to TCA. Within the group of TCAs, nortriptyline has been recommended, partly due to less pronounced cholinergic effect, and partly due to the fact that it is possible to measure the concentration in the blood and thus reliably determine the right dose.

Amitriptyline, nortriptyline, desipramine and clomipramine have not been found in the blood of nursed infants, and no side-effects in the child are described. Doxepin has been associated with symptoms of the child, including drowsiness and vomiting. Dosulepin is measured in breast milk as well as in the blood of nursed children, but no side-effects in the child have been reported. Maprotiline can be measured in breast milk, but otherwise only scarce data are available. It is uncertain whether TCA affects the brain development. There are no signs of serious problems in their childhood after exposure in the pregnancy assessed on the basis of two studies with a total of 116 exposed (66).

**Treatment with monoamine oxidase inhibitors.** Not recommended due to insufficient data.

**Treatment with agomelatine.** Not recommended due to insufficient data.

**Treatment with vortioxetin.** Not recommended due to insufficient data.

**Bipolar affective disorder.** At least 40 000 Danes are affected by bipolar affective disorder.
What is mania? In the manic phase, the mood is elevated, and the person is most often described as being ‘all keyed up’ with abnormally elevated energy level and as being socially flattering and charming bordering towards a socially inappropriate behaviour with a lack of understanding of limits. The manic phase is divided into degrees of severity: hypomania, moderate mania and severe mania. Generally, mania can occur very suddenly and develop either in a few hours or in a few weeks.

In the hypomanic (mild manic) phase, the person is more active, committed and energetic than usual. At the same time, the person is more optimistic, outgoing and speaks more. However, there may also be an increased tendency towards irritability. Many people with bipolar disorder describe the hypomanic state as being very productive and actually a good state to be in.

In a moderate manic phase, the symptoms increase in strength. The person is hyperactive, has several projects running at the same time, and is restless and uneasy, and the need for sleep is often decreased. There may be an increased ideation and problems with sticking to one subject at a time. The person can easily lose the thread and be distracted. Some people become more intrusive, irritable or angry if their many ideas are rejected. The person is usually excited, has an increased self-esteem, may experience an increased sexual desire and develop an increased spending of money without thinking about the consequences. In the same way, some people begin to behave irresponsibly and recklessly.

In the severe manic phase, the symptoms are extremely pronounced: the person sleeps no more than 3–4 h, is in constant activity, is out of control and has a feeling of being invincible. The condition can be associated with severe anxiety, but the person can also be threatening, aggressive and explosive. In some cases, there may be psychotic symptoms such as delusions and hallucinations. In untreated cases, a mania can result in so-called acute delirium, which is a life-threatening condition in which the person is extremely troubled and restless, the body temperature rises and the person may lose a lot of fluid. At worst, the condition can result in circulatory collapse and death.

The risk of not treating the bipolar condition in pregnant women. The risk of relapse of depression or mania seems to be highest in month 4–9 of the pregnancy. Some studies find that approximately 35% experience relapse despite medical treatment, whereas 85% experience relapse without drugs, primarily in the shape of depressive episodes or mixed episodes with both manic and depressive symptoms at the same time (67). If the mother is not treated, the foetus can risk being exposed to larger concentration of stress hormones, especially if the patient with bipolar condition is destabilized. Disorder breakout in the mother can have serious consequences for her child, as it results in an increased risk of excessive use of alcohol, tobacco and illegal drugs, poor nutrition, sexually transmitted diseases, suicide, reduced maternal care for the child and physical violence against the child (19, 68–71).

Medical treatment of women of child-bearing age with bipolar disorder. The possibility of pregnancy should always be discussed with this group of women. Furthermore, psychotropic drugs specifically problematic during pregnancy, such as valproate and carbamazepin, should be avoided. Evidence of the preventive effect is poor for valproate and carbamazepin, which is why they should primarily be used in the treatment of acute mania if other treatments have appeared to be ineffective or not tolerated (72). At the same time, it must be ensured that the woman is not pregnant. Valproate also increases the risk of polycystic ovary syndrome, which can cause irregular periods and infertility. Oral contraceptives should be taken into consideration in the event of valproate treatment, partly to inhibit the development of polycystic ovary syndrome, partly as safe contraception. At start-up and discontinuation of oral contraceptives containing oestrogen, it has to be taken into consideration that the oestrogen increases the

Psychotropic drugs during pregnancy and breast-feeding

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breakdown of lamotrigine by approximately 50%. Antipsychotics may increase prolactin and result in infertility. This is specifically evident in connection with risperidone and typical antipsychotics, but can occur in all antipsychotics (73).

Treatment with mood stabilizers

Recommendations. Planned pregnancy and start-up during pregnancy.

i) Prescription and control of the patient’s treatment should be performed in collaboration with a specialist in psychiatry, ideally in a specialist clinic in the regional psychiatric.

ii) Lithium is still a cornerstone in the treatment of bipolar disorder, and as the absolute risk of teratogenic damage is small, it is recommended to use lithium if an overall assessment finds an indication for mood-stabilizing treatment during pregnancy.

iii) Valproate and carbamazepin are contraindicated during pregnancy due to the high risk of neural tube defects.

iv) In bipolar disorder with primarily or exclusively manic episodes, lithium, olanzapine, risperidone, quetiapine and clozapine can be used. Alternatively perphenazine*.

v) In bipolar disorder with primarily depressive episodes or without manic episodes during many years, lamotrigine may be used. In general, use of doses up to 300 mg is recommended. Special caution is recommended in the case of higher doses, where serum measurement is recommended each month.

vi) Antidepressants are generally not recommended in bipolar disorder, as the effect of this is much debated.

Pregnancy occurring during an existing treatment. The patient should be assessed by a specialist in psychiatry. The indication for medical treatment during pregnancy of women with bipolar disorder depends, among other things, on the following factors:

i) The general evidence of the effect of maintenance treatment of various drugs.

ii) The generally increased risk of relapse/development of new episodes during and after pregnancy with and without mood-regulating drugs.

iii) Risk of teratogenic damage for the individual drugs.

iv) The individual patient’s course of illness (time of onset, current age, the number of illness episodes, type and severity of affective episodes, any previous course of pregnancy).

v) Effect and possible side effects of mood-stabilizing drug for the individual patient.

On the basis of items 1–5, a professional assessment of the patient’s individual risk of affective episodes vs. teratogenic damages is made, forming the basis for the decision of the patient and spouse regarding medical treatment during pregnancy.

Background. Pharmacological treatment of bipolar disorder during pregnancy is a highly specialized function, which according to the Danish Health and Medicines Authority should only be undertaken in specialist clinics for affective disorders. Guidance in medical treatment of pregnant women requires thorough knowledge of the patient and the specific illness course, of special risk factors and of the treatment. This should take place in close cooperation with obstetrics wards.

Pregnancy does not protect against new episodes, and discontinuation of mood-stabilizing drugs during pregnancy increases the risk of relapse considerably (67). In principle, it is recommended to use the lowest possible effective dose of mood-stabilizing drug as well as to use as few drugs at the same time as possible. One must be aware that an increase of dose often is necessary in the third trimester, where the blood volume is increased by approximately 30% (74). Plasma monitoring is recommended, for example with blood test every month, among other things because several of the liver’s enzyme systems have increased activity during pregnancy, which means that for instance, lamotrigine breaks down more quickly.

As the plasma volume and the kidneys’ filtration speed are increased during pregnancy and normalized immediately after the birth, it means that it may be necessary to increase the lithium dose during pregnancy and similarly reduce immediately after the birth.

General evidence of the effect of maintenance treatment of various drugs. The evidence of maintenance treatment can be summed up on the basis of new guidelines from the World Federation of Societies of Biological Psychiatry (75). Lithium is the drug with the best evidence for a mood-stabilizing

*After Trilafon (perphenazine) has been deregistered in Denmark, patients can be treated with the similar drug Peratsin instead. The medical doctor may apply for general permission to prescribe Peratsin ‘Orion’ 2, 4 and 8 mg via the Danish Health and Medicines Authority (http://laegemiddelstyrelsen.dk/da/topics/godkendelse-og-kontrol/udleveringstildadelser). A copy of the permit is handed out to the patient, and the pharmacist can then hand out the drug.
effect in bipolar disorder. Lithium, shown mood-stabilizing effect in relation to the prevention of depression, mania and mixed episodes, whereas there is less evidence that olan- 
vapine prevents depressive episodes. Aripiprazole does not prevent depressive episodes, but only manic and mixed episodes, like all other atypical antipsychotics. Valproate is effective in the event of acute mania, whereas the evidence of the pre-
ventive effect on mania is poor. Lamotrigine pre-
vents in particular depressive episodes.

General risk of relapse/development of new episodes during and after pregnancy with and without mood-stabi-

lizing drugs. No randomized studies are available, which have compared the effect of mood-stabilizing medical treatment versus no treatment during pregnancy. However, there is a consid-
erable risk of development of affective episodes dur-

ing and after pregnancy.

During pregnancy. The largest and best conducted study is from Viguera et al. In a prospective non-

randomized trial, they found that 71% of a total of 89 women with a known bipolar disorder devel-

oped a new affective episode during pregnancy (67). Most episodes were depressive or mixed epi-

sodes, and 47% appeared in the first trimester. Women who discontinued with medical treatment immediately before pregnancy had two times increased risk of developing new episodes and were ill five times as many weeks during pregnancy compared with women who continued the mood-stabi-

lizing medical treatment.

After pregnancy. A Danish register-based study showed that 26.9% of women with known bipolar disorder were hospitalized within a period of 1 year after the birth of the child. The greatest risk of hospitalization was 10–19 days after the birth (76). Patients with bipolar disorder have an increased risk of developing a postpartum psy-

chosis (77), particularly in the first 4 weeks after the birth of the child. The risk of relapse is eight times higher in the first months after the birth, which increases the need for close follow-up and support in this period. In the event of acute mania during pregnancy, antipsychotics or ECT is used, which does not affect the foetus inappropriately, and which is described further in a later section.

Risk of teratogenic damage for the individual drugs. Lithium: The risk of Ebstein’s anomaly (right ventricular hypoplasia and displacement of the tricuspid valve) in children is 1 : 20 000. In children exposed to lithium in the first trimester, the risk seems to be between 1 : 1000 and 1 : 2000, which is 10–20 times increased compared to the risk of the background population (71, 78–80), but in absolute figures still a very small risk. A recent meta-analysis published in Lancet identified 62 studies of possible teratogenic effects of lithium (81). The risk of Ebstein’s anomaly was not statistic-

ally significantly increased among children exposed to lithium compared to the risk among unexposed children, but the estimate is uncertain due to the low number of cases with Ebstein’s anomaly. The article also refers to a case–control study of children born with malformations in general, which did not find statistically significantly more women treated with lithium in the malforma-
tion group (6 of 10 698) compared with the control group of children without malformations (5 of 21 546) (82). Lithium must still be considered a cornerstone in the treatment of bipolar disorder, and as the absolute risk of teratogenic damage is small, it is recommended to use lithium if an over-

all assessment finds an indication for mood-stabi-

lizing treatment during pregnancy (83).

Antiepileptics: Generally, there is a correlation between dose and the risk of malformations, which is why it is important to evaluate whether the preg-
nant woman can be treated with a lower dose dur-

ing pregnancy (84).

Lamotrigine: Lamotrigine used as monotherapy appears to constitute a low risk (71, 85, 86), even though a few reports as the North American Antiepileptic Drug Pregnancy Register indicate an increased risk of cleft lip and palate increasing from 1 : 500 among the population to 1 : 120 (87, 88). The risk seems to be increased in a dose of more than 300 mg/day (89, 90), as the risk of heart malformations and hypospadias increases to 1%. The plasma level of lamotrigine falls by 60–65% in second to third trimester (90, 91) and should be monitored closely during the pregnancy, for example with blood test every month. After the birth, the serum concentration of lamotrigine increases again. Prophylactic treatment with folic acid (5 mg daily) should be initiated in case of pregnancy wish to prevent neural tube defects. Treatment with folic acid will continue in the first trimester (92). In general, use of lamotrigine up to 300 mg is recom-

mended. Special caution is recommended in the case of higher doses, where serum measurement is recommended each month.

Valproate and carbamazepine: The risk of neural tube defect using carbamazepine over 1000 mg is 2% (90). When using valproate below 700 mg, the risk of neural tube defects is 1% and over 700 mg 2%. When using over 1500 mg valproate, the risk of multiple malformations is 7%, of heart malfor-
mations is 7% and of hypospadias is 5%. Valproate may possibly affect the foetal brain, and a high association between valproate exposure in utero and later risk of autism is found (93). The use of valproate and carbamazepine is contraindicated during pregnancy.

**Breast-feeding. Lithium:** RID is very high, between 72 and 30%. Nursed children achieve plasma which is up to 24–72% of the mother’s (94). Use of lithium during breast-feeding is usually not recommended, but the drug can be used under close observation of the child and possibly guided by measurements of the concentration of lithium in the breast milk. Lithium can lead to dehydration, exhaustion, hypotonia and electrocardiographic changes in the child.

**Valproate:** Breast-feeding is possible. RID is 1–2%. No side-effects have been described in nursed children.

**Carbamazepine:** Breast-feeding is possible. RID is 4–6%. No side-effects have been described in nursed children.

**Lamotrigine:** Breast-feeding is possible at doses of no more than 200 mg daily. RID is relatively high from 9 to 18%. Nursed children achieve plasma concentrations of approximately 30% of the mother’s. Many courses without side-effects in nursed children are described. One case of neonatal apnoea is described where the mother had 850 mg daily.

Generally, antidepressants should not be used in bipolar disorder, as it is still being debated whether there is evidence for this (95).

**Psychoses.** This group of disorders is divided into three subgroups consisting of schizophrenia, acute psychoses and chronic psychoses. Around 25 000 people in Denmark are diagnosed with schizophrenia. In the course of a lifetime, 1% of the population will be diagnosed with schizophrenia. For the majority of people with schizophrenia, the disorder manifests itself between the ages of 16 and 25 years, but the disorder is also seen in children and elderly. The gender distribution is equal, however, with a tendency that women have a higher age at onset and a milder course than men. The disorder affects the ability to think, feel and perceive reality correctly, and there will often be problems with entering into relations with others. The most noticeable symptoms are hallucinations and delusions. By hallucinations, the person, for example, hears voices which speak about the person in question, and hallucinations in other sensory forms may also occur, for example olfactory, gustatory and tactile. Delusions are characterized by an unshakable conviction which is considered unrealistic or impossible. The delusions are grouped according to which theme they concern, for example persecution, megalomania, physical illness etc. A psychosis increases the risk of suicide, social isolation and exclusion from the labour market.

The risk of not treating the psychotic condition in pregnant women. The risk of a non-planned pregnancy is increased in women with psychotic disorders. Approximately 60% of women with such a condition will carry out a pregnancy (96–98). Data on the risk of relapse of psychotic symptoms in pregnant women with a general psychotic disorder are not present, but the risk of relapse is 65% in pregnant women with schizophrenia. The attending medical doctor should inform the woman of risks of the current treatment already before any pregnancy, explain about a possible need for change of medicine during pregnancy and inform her about the risk of abrupt discontinuation of medical treatment, such as insufficient nutrition, pregnancy complications and an increased risk of drug abuse (99).

If the woman has a desire for pregnancy, but the medical treatment is considered suboptimal in relation to this, safe contraception must be agreed upon until changes in medical treatment have been made, and the initial risk of relapse by change of medicine is over. If the woman is already pregnant, a detailed plan must be made for collaboration between relevant parties, such as own medical doctor, psychiatrist, obstetrician and municipal partners.

In the treatment with antipsychotics, an increase in prolactin can be seen. The risk is highest in first-generation antipsychotics and risperidone, amisulpride and paliperidone. The increased prolactin levels may cause breast tension, milk secretion, irregular periods and reduced fertility.

In addition to focus on the pharmacological treatment, the psychosocial support for the woman must be optimized to ensure that the pregnancy runs as smoothly as possible and to minimize the risk of recurrence of the psychotic symptoms. After the birth of the child, psychological conditions in connection with expectations and fear from the woman and her family as well as the physical and psychological pressure to care for a newborn can contribute to an increased risk of relapse.

Medical treatment of women of child-bearing age with psychotic disorder. An increased incidence of premature birth has been described among people treated with antipsychotics, but it is unclear whether this is due to the pharmacological treat-
ment, or whether it is an expression of the underlying illness (100, 101). However, the risk is not increased by the use of atypical antipsychotics as opposed to the use of first-generation antipsychotics. This may, however, be due to the fact that it is the most seriously ill women who use first-generation antipsychotics (100, 101). Addition of anticholinergics against side-effects from antipsychotics appears to increase the risk of malformations and should if possible be avoided (102).

There are known metabolic side-effects of antipsychotics, but the risk of metabolic complications in the newborn has not been clarified (100, 103, 104). An increased risk of hypoglycaemia in newborns has been found if the mother has been treated with atypical antipsychotics during the pregnancy (103, 104). The metabolic side-effects from treatment with antipsychotics should be assessed on an ongoing basis in the mother, as the risk of diabetes is increased.

In children who have been exposed to antipsychotics during the foetal stage, increased waking state, restlessness, crying and sleep problems (histaminergic rebound) and increased saliva secretion and diarrhoea (anticholinergic rebound) immediately after the birth can be observed.

Treatment with antipsychotics

Recommendations. Planned pregnancy and start-up during pregnancy. Olanzapine is primarily recommended based on the amount of safety data. Other conditions may, however, be of importance for the choice of drug, including metabolic risk profile. Earlier, perfenazine was recommended, but data for olanzapine, quetiapine and risperidone are comparable with this and do not indicate an increased risk of congenital malformations. ECT may be considered.

Pregnancy occurring during an existing treatment. The pregnant woman will most often be in treatment with an atypical antipsychotic. As described below, data for a number of medicinal products are available, and the need for change will depend on a specific assessment of the patient’s risk of recurrence compared to the product’s risk profile.

Breast-feeding. RID is typically in the range of 0–2% for most of the antipsychotics, and side-effects in nursed children are only described exceptionally. Factual data for all the drugs, however, are not available (14). We refer to the specific drug descriptions below.

Background. Prescription and control of patients undergoing treatment with antipsychotics should be performed in collaboration with specialist in psychiatry. In 2011, FDA issued a general warning in relation to the use of antipsychotics during pregnancy, primarily due to an increased incidence of extrapyramidal symptoms and discontinuation symptoms (9). The first symptoms indicate that the brain of the child as well as of the mother is affected. The data volume for use during pregnancy is significantly smaller for antipsychotics compared with antidepressants, and in fact, only olanzapine meets the requirements of this guideline’s formal criteria of more than 1000 exposed pregnant women. The body’s enzyme systems have increased activity during pregnancy, which may lead to olanzapine and clozapine being metabolized quicker than normal. Certain antipsychotics, such as haloperidol and perfenazine, have a reasonable defined therapeutic window, which is why it is recommended to regularly measure antipsychotics in the blood, for example every 3 months during the pregnancy.

An increased incidence of premature birth has been described among women treated with antipsychotics, but it is unclear whether this is due to the pharmacological treatment, or whether it is an expression of the underlying illness (confounding by indication) (100, 101).

Newer antipsychotics. Pregnancy. Olanzapine: Olanzapine is the newer antipsychotic with the most data for use during pregnancy. Data for about 1100 first trimester exposed show no signs of excess incidence of undesired foetal impact (105, 106). Treatment with olanzapine during pregnancy can be used if there is a clear indication for this. Dose during the last part of the pregnancy should be kept as low as possible. A case report has found an increased risk of changed glucose tolerance during pregnancy in the mother (107).

Quetiapine: About 450 cases of pregnant women treated with quetiapine have been reported. No pattern of malformations which could indicate a specific teratogenic effects of quetiapine is observed, and no increased prevalence of malformations compared to baseline risk is seen (8, 105, 108, 109). The safety and the effect of quetiapine during pregnancy are insufficiently described, and the treatment is not recommended as a rule. However, there may well be clinical courses, where it is not rational to switch from an efficient ongoing treatment with quetiapine.
Aripiprazole: Not recommended during pregnancy due to insufficient data.

Risperidone: Data for more than 400 first trimester pregnant women treated with risperidone show no increased risk of malformations (8, 105, 108). As a rule, risperidone is not recommended during pregnancy, as the safety is inadequately established. However, there may well be clinical courses, where it is not rational to switch from an efficient ongoing treatment with risperidone.

Paliperidone: Not recommended due to insufficient data. There are few specific data, but extrapolation from risperidone data is to some extent acceptable, as paliperidone is the active metabolite of risperidone.

Clozapine: About 200 cases of pregnant women treated with clozapine have been reported. No pattern of malformations is observed. Clozapine is not recommended due to insufficient data. It can be clinically indicated to use clozapine during pregnancy for women who have had no effect of another treatment, and who therefore cannot be switched to one of the recommended antipsychotics.

Ziprasidone: Not recommended due to insufficient data.

Breast-feeding.

Olanzapine: Can be used. RID is below 2%, and no side-effects have been described in nursed children.

Quetiapine: Can be used. RID is below 1%, and side-effects in nursed children are not reported.

Aripiprazole: Can be used. RID is below 1%, and side-effects in nursed children are not described.

Risperidone: As a rule, not recommended. RID is between 3 and 9%.

Paliperidone: Not recommended due to insufficient data.

Clozapine: As a rule, not recommended. RID is below 2%, but because of the side-effect profile, clozapine is not recommended during breast-feeding (14, 110).

Ziprasidone: Not recommended due to insufficient data.

Older antipsychotics. Pregnancy.

Perphenazine: Data exists for 500 exposed without signs of increased incidence of undesired foetal impact. In addition, there are some data for perphenazine administered in lower doses as an antiemetics.

Haloperidol: Not recommended. Data exist for about 300 first trimester-exposed without signs of significantly increased incidence of malformations.

One child of 188 lacked development of left hand (111).

Amisulpride: Not recommended due to insufficient data.

Breast-feeding.

Perphenazine: As a rule, breast-feeding is not recommended. There are insufficient data for transfer into the breast milk, but in one case, however, the transfer of perphenazine was found to be low (112).

Haloperidol: Breast-feeding is not recommended. RID is poorly defined – up to 12% in one study.

Amisulpride: Breast-feeding is not recommended due to insufficient data.

Treatment with anxiolytics and hypnotics

Recommendations. Planned pregnancy and start-up during pregnancy. It is recommended to avoid benzodiazepines during pregnancy if possible, as the results of the available data are conflicting regarding the risk of malformations. As hypnotic, zolpidem and zopiclone can be used for a short period.

Pregnancy occurring during an existing treatment. Benzodiazepines are not recommended during pregnancy. It must be considered whether phasing them out can be planned. If using them, whether the mother can carry out a pregnancy without the drugs must be balanced against the risk for the child.

Birth. Use close to birth can result in discontinuation symptoms in the child or a limp child who is affected by the drug.

Breast-feeding. Benzodiazepines during breast-feeding are not recommended due to the risk of drowsiness of the child.

Background. If the treatment with anxiolytics or hypnotics during pregnancy is deemed necessary, the data volume is largest for diazepam. Due to the risk of withdrawal symptoms in the newborn child, the treatment with fixed scheduled doses of benzodiazepines should be avoided in the last month of the pregnancy.

Hypnotics. The hypnotics zolpidem and zopiclone are not actual benzodiazepines. Data exist for more than 1000 exposed children (8) without signs of an increased incidence of malformations, whereas an abstract has described an increased incidence of miscarriages and premature birth.
Any treatment with these hypnotics should be of short duration.

**Benzodiazepines.** Benzodiazepines and benzodiazepine analogues are frequently used as add-on treatment in patients with a mental disorder. Benzodiazepines are also used in patients who have not been diagnosed with a mental disorder, however, more often in a short period.

A study with data from the Swedish Birth Register found 1979 children who had been exposed to benzodiazepines during the pregnancy. The conclusion of this study was that maternal use of benzodiazepines may increase the risk of low birth weight or premature birth and cause symptoms at the birth in the shape of drowsiness, but no strong teratogenic potential is found, in relation to neither cleft lip nor palate. The same is found in an American cohort study of 2793 women (114, 115). A meta-analysis of 1 051 376 persons, of which 4342 were exposed to benzodiazepines in the first trimester, examined the risk of malformations in general and of heart malformations and did not find an increased incidence (116). In the study, benzodiazepines were analysed as a group and not as single drugs. A systematic review of Bellantuono analysed the individual drugs (117), but due to the scarce data, no clear recommendation can be made.

Previous studies have raised suspicion of an increased risk of cleft lip and palate by exposure to individual benzodiazepine drugs during first trimester of the pregnancy (118). Exposure to clonazepam has been reported in 140 cases without an increased risk of malformations being found, whereas exposure to chlordiazepoxide in a study of 201 patients was associated with an increased incidence of heart malformations (119), a result which is not confirmed in a smaller study of 88 depressed patients who took chlordiazepoxide in high doses for suicidal purposes (117). Chlordiazepoxide is used for instance in detoxification in relation to alcohol abuse. This means that to a high extent, there is a risk of confounding by indication when the risk of the foetus is assessed.

Studies of the use of diazepam are ambiguous, as some studies show an increased risk of malformations of arms and legs, rectal/anal stenosis/atresia, heart malformations and other congenital malformations (117). A subanalysis of data, where only women who had been prescribed diazepam were included, found no increased risk of malformations. In the last part of the analysis, women who had self-reported the use of the drug were excluded. One of the reasons for the described increased risk could be recall bias.

Use of nitrazepam is described for 100 women who took an overdose of the drug (120) and an increased risk of malformations as well as a significantly increased risk of miscarriage are found.

Use of lorazepam and bromazepam is associated with an increased risk of anal atresia (OR 6.19) and other malformations in the intestinal system (OR 6.15) compared with other benzodiazepines (117), but the absolute risk of exposure is, however, still very low with a NNH around 590. A British study from 2014 of more than 375 000 live births found that the risk of major malformations in general was 2.7%, whereas the risk of using different benzodiazepines did not increase the general risk of malformations (121).

The malformations described have not suggested a specific pattern of malformations of the individual drugs. The importance of recall bias and confounding by indication is unclarified for most of the described studies, as data are often based on reports of side-effects and malformations.

If there is indication for the use of benzodiazepines in the first trimester, use of diazepam is considered most safe (117). When using benzodiazepines later in the pregnancy, the risk of drowsiness and overdose of the newborn must be taken into consideration with special focus on the extended half-life in preterm infants (122). By use of high doses of benzodiazepines, an increased risk of miscarriage has been found for alprazolam, diazepam, chlordiazepoxide and nitrazepam when examining patients who have attempted suicide with the mentioned drugs.

**Brain development and emotional development.** Use of benzodiazepines and their influence are not widely examined.

**Treatment with pregabalin**

**Pregnancy.** Pregabalin is a relatively new drug. The data are insufficient, for which reason it cannot be recommended during pregnancy.

**Breast-feeding.** There are no data for transfer into the breast milk, and breast-feeding is not recommended.

Pregabalin is used to treat anxiety disorders, cramps and fibromyalgia and is released unchanged via the kidneys. The release is probably increased during the pregnancy, but no larger studies are available. In newborns, the half-life is 14 h instead of the usual 5–7 h for pregabalin.

**ADHD.** AD stands for attention deficit and H for hyperactivity and D for disorder. About one-third

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of all with this illness is without hyperactivity and impulsivity, and the diagnosis can thus be particularly difficult to make. This condition is called ADD.

ADHD is seen in approximately 3–5% of all children. The symptoms change with age, and most of the affected will become, for example, less restless. Therefore, only 2–3% of the adult population is expected to have ADHD in a noticeable degree. ADHD has long been known and treated in children. To make the diagnosis in adults, the symptoms must have been present before the age of 7, and they must have been permanent until adulthood.

Persons with ADHD will often be characterized by impulsive behaviour, lack of perseverance and conflict-ridden relations to the surroundings, and they have an increased risk of developing other mental disorders such as depression, anxiety and OCD personality disorder or abuse (123).

The risk of not treating ADHD in pregnant women. Women with ADHD often have worsening of ADHD symptoms premenstrually. On the other hand, the symptoms often diminish during pregnancy, which has the advantage that you will most often be able to take a break from the central nervous system (CNS) stimulants, drugs that speed up physical and mental processes, without major problems without major problems (123).

Treatment with methylphenidate and atomoxetine

Recommendations. Planned pregnancy and start-up during pregnancy. As a rule, the treatment is not recommended. In case of disorder requiring treatment, methylphenidate should be preferred.

Pregnancy occurring during an existing treatment. The treatment indication should be considered. Atomoxetine treatment should be discontinued, alternatively switched to methylphenidate.

Background. Methylphenidate. Pregnancy: In all, data are available from more than 500 first trimester-exposed pregnant women without signs of increased incidence of congenital malformations. A Danish overview article described 180 children exposed to the risk of methylphenidate and found four heart malformations (including two ventricular septal defects and one with univentricular heart) corresponding to a risk of 2.2%, which should be compared with the risk of the background population of 3.5%. A recent Danish register study, whose data do not overlap the data in the above-mentioned study, found no increased incidence of congenital malformations in 220 children exposed in the first trimester (124).

Breast-feeding: For methylphenidate, RID is below 1%. No side-effects have been described in nursed children.

Atomoxetine.

Pregnancy: The data volume for atomoxetine is insufficient, and treatment with this drug is therefore not recommended.

Breast-feeding: Atomoxetine is not recommended due to insufficient data.

ECT for pregnant and breast-feeding women

Recommendations. Planned pregnancy and start-up during pregnancy. Depending on the degree of the mental illness, first talk therapy and medical treatment will be offered. ECT for pregnant women, however, is considered an effective treatment, which very rarely causes problems in relation to the pregnant woman or the foetus. It is a treatment which must be carefully considered in pregnant women with severe symptoms, such as psychotic depression, high risk of suicide or catatonia which may be life-threatening.

Breast-feeding. There are no problems in using ECT to breast-feeding women, except that the child must be observed for, whether it is affected by the drug which the mother has been anaesthetized with.

Background. With ECT, you avoid long-term medical treatment, which may affect the unborn child, and at the same time, the treatment is very effective. However, only scarce reports exist shedding light on the question of efficiency and side-effects of the mother and the foetus. Thus, the literature reports around 340 cases where ECT has been used for pregnant women (125).

Effect of ECT treatment. In the cases where the effect of the treatment has been stated, the total incidence of partial and full response was 84% for depression with or without psychotic symptoms. When schizophrenia or schizophreniform disorder was treated, the frequency of at least partial
response was 61%. These response rates as well as the average number of treatments at 10.7 correspond to the conditions in non-pregnant women. Thus, the treatment is by all accounts extremely efficient assessed on the basis of this relatively modest material.

Side-effects in the foetus. Out of 339 cases, 25 cases of abnormalities in utero and at birth have been described, but in many of these cases, the abnormality probably arose before or long after the ECT treatment. In 11 cases, the complications were probably related to ECT. The most common complication was 8 cases of temporary low pulse. The only death, which this overview article connected with ECT, was a case where the mother had long-term seizures (status epilepticus) secondary to the treatment (125). Nine deaths are considered to be non-related to ECT, namely one newborn had peritonitis and died 8 weeks after the last treatment, two died due to congenital transposition of the large blood vessels, which had been seen by ultrasound before ECT, and one died 2 days after the birth several months after the last ECT. One foetus died in a car accident, and three died of congenital abnormalities leading to a cyst in the lungs and a total lack of development of the brain. The latter cases are probably not related to ECT, as the treatment was used in the second and third trimester and not in the first trimester, where the organs are formed. A case report from 2007 described the birth of a child with multiple haemorrhages in the brain, where the mother had received seven ECT in the weeks 20–34.

Cardiac arrhythmia in utero. Regarding non-mortal abnormalities, there were 8 cases of arrhythmias in the foetus, for example decelerations in the cardiotocography (CTG, the electronic monitoring of foetal heart rate and the contractions of the woman in labour) which are suspected to be related to ECT. The arrhythmias occurred at a frequency of approximately 2.7% and were probably caused by low oxygen supply. However, it is not stated whether the woman prior to the treatments were ventilated with pure oxygen, which is the procedure today.

Side-effects in relation to the mother. Twenty women had complicated pregnancies in connection with the ECT treatment: partly the above-mentioned case of long-term seizures (status epilepticus), partly cases of blood in the urine (haematuria), a miscarriage and contractions or premature birth, and finally, one case of vaginal bleeding, abdominal pain and abruptio placentae.

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It cannot be ruled out that some of these complications might be related to ECT.

Braxton Hicks and initiation of birth. In 3.5% of the cases, contractions or premature birth was reported. This is not caused by the electric current from the ECT apparatus, because it does not pass through the uterus, but may possibly be due to release of the hormone oxytocin from hypothalamus. In the event of contractions, beta-adrenergic agonists can be used to stop them.

Recommendations on the basis of the literature. Prior to the treatment, an obstetrician is conferred with among other things with regard to monitoring the foetus with CTG, and whether the treatment is to take place in maternity ward.

Positioning of the mother. It is presumably important that women in late pregnancy are positioned with a slightly elevated right hip, so that the uterus is pushed to the left, and pressure on the large vessels in the body (aorta and vena cava) is avoided. This will result in improved blood flow of the placenta.

Anaesthetics. The most commonly used anaesthetics in Denmark are barbiturates, although propofol is also used occasionally. Both types of drugs work with very short half-lives, cross the placental barrier and can be found in the foetus’ blood. There is no suspicion of teratogenicity, but the use of the drugs must of course be avoided immediately before the birth, because they can dull the child. The seizure activity is usually attenuated with succinylcholine, which, however, hardly crosses the placenta and has no known teratogenic effects.

Hyperventilation to reduce the seizure threshold should, however, be avoided, as this would lead to alkalosis, which complicates the transport of oxygen from the mother’s haemoglobin to the foetus’.

Aspiration risk. It has been suggested that pregnant women who received ECT had a greater risk of aspiration from the ventricle. However, among the cases described in the literature there are no cases of pneumonia caused by aspiration. Some hospitals tend to increase pH in the stomach, for example by giving sodium citrate or similar antacid 15–20 min before ECT. If atropine is given prior to the treatment to prevent slow heart rate (brady-cardia), this may result in poorer oesophageal closing off and may in principle increase the risk of aspiration. Therefore, use of atropine in pregnant women is not recommended. In women with
known high risk of acid reflux, endotracheal intubation can be performed.

The actual seizure. As mentioned before, no power runs through the uterus during stimulation. The mother’s seizures during ECT are not as such harmful to the child, but low oxygen saturation may, of course, be. Therefore, it is important to limit the length of the seizure if it is prolonged, just like an extended seizure condition (status epilepticus) of course must be able to be treated. First choice will most often be diazepam. Normally, the woman will, however, not experience low oxygen saturation during the seizure, which can be determined by pulse oximetry, and the child will therefore not be missing oxygen (126–128).

Discussion

Bias and confounding

The above-described problem concerning the quality and validity of available data makes this topic extremely sensitive to bias. Important biases, which can complicate the interpretation of data, are described as follows.

Confounding by Indication. Is it the treatment or the disease itself which increases the risk of undesired foetal impact? This is a difficult problem which is not always easy to solve despite sophisticated epidemiological methods (6, 7, 129). Above the individual diseases, the risk of not treating the disease in question is reviewed. An example of this problem should be mentioned here: A Danish register study found that the risk of malformations was increased from the normal 3.5–5% in pregnant women undergoing treatment with an SSRI and increased from 3.5–4.5% in pregnant women who discontinued with a SSRI at least 3 months before the pregnancy (1). The increased risk could indicate confounding by indication. For example, depression is known to be associated with an unhealthy lifestyle (smoking and alcohol consumption) as well as poor utilization of the offers of the pregnancy care. In the above-mentioned study, no connection between dose and the risk of malformations is established.

Recall bias/misclassification of exposure. Some data collection takes place by contacting the pregnant women long after the exposure to a given drug. There is a risk that women giving birth to healthy children are less likely to remember exposure to drugs as women giving birth to children with malformations. However, this kind of bias is minimized a great deal in more recent pharmacoepidemiological studies.

On the other hand, one is dependent on valid and complete information in the available registers containing information on congenital malformations and other unwanted pregnancy outcomes (6, 7, 129). If prescription statements are used, one cannot be sure that the pregnant woman has actually taken the collected drug.

Publication and citation bias. Of course, a general and fundamental bias is the fact that positive scientific findings are easier published than negative. However, within the area of this report, it has considerable serious consequences, as a positive signal announced once is very difficult, in practice, to exorcise despite several subsequent negative studies. Thus, an early published signal will often be cited to a considerable extent, although later studies cannot confirm the original results. This means that the results from an early published, typically smaller scale study with a positive signal for a given malformation will be elevated to contain a truth value very difficult to reverse (130–132).

Ascertainment bias. Diagnosing heart malformations represents a specific problem. The frequency of congenital ventricular septal defect (VSD), is around 0.5%. Often, these are of no clinical significance and close spontaneously without having been diagnosed. With recent years’ focus on heart malformations and SSRIs, there is a high risk that children born to mothers in SSRI treatment will be subjected to echocardiography where a malformation will be discovered which you do not know the importance of and which would not otherwise have been detected. This ascertainment bias is documented in a Canadian study (133). It will pull in the opposite direction if a heart abnormality for instance increases the risk of miscarriage or often leads to termination of the pregnancy if it is detected prenatally. In this way, an underestimation of the risk will occur.

Stratification and multiple testing. These are necessary scientific and statistical tools which contribute to shedding light on the studied contexts and generate hypotheses. These techniques are, however, also double-edged swords which may compromise a clinically meaningful interpretation of the data:

i) A Danish population study of the use of SSRI during pregnancy (40) found no significant increased risk of congenital malformations in 1370 children of pregnant women exposed to an SSRI in the first trimester, OR 1.21 (95% CI
There was no significantly increased risk of congenital heart malformations as OR was 1.44 (95% CI 0.86–2.40). By further stratification of five different specific heart malformations, however, a signal for ventricular septal defect, OR 1.99 (95% CI 1.13–3.53), was observed.

ii) A Finnish population study of the use of SSRI during pregnancy (38) found no significantly increased risk of congenital malformations in 6881 children of pregnant women exposed to a SSRI in the first trimester, OR 1.08 (95% CI 0.96–1.22). The publication mentions no less than 96 odds ratios with associated confidence intervals for general and specific estimates of connections between SSRI drugs and specific malformations, including 7 odds ratios for specified heart malformations. Among the 96 analyses, three statistically significant associations were present:

a) Paroxetine and right outflow tract defects (3 cases), OR 4.68 (95% CI 1.48–14.74).

b) Fluoxetine and isolated VSD (19 cases), OR 2.03 (95% CI 1.28–3.21).

c) Citalopram and neural tube defects (absolute number is not specified), OR 2.46 (95% CI 1.20–5.07).

Typically, such positive results will be mentioned in abstracts and find their way to the media. Those kinds of studies are published constantly. Of course, they contribute considerably to our total amount of knowledge, but if you react uncritically on every result of this type, there is a high risk of over-interpretation with unfortunate noticeable clinical consequences as a result. Interpretation of such analyses is difficult, especially if they are not specifically defined in advance as the results in this case, in principle, are only hypothesis generating. Regardless of the results, they should be replicated in other studies before any clinical significance can be reasonably attributed.

Regulatory matters. The summary of product characteristics (SPC) is an integrated part of the marketing authorization. The SPC binds the manufacturer in relation to the marketing, but it is not binding in relation to the medical doctors’ clinical use of the drug, or in relation to use during pregnancy. The SPC is based on the available knowledge on a given drug at the time of the introduction (134). With regard to use of the drugs during pregnancy, typically only few human data are available, and reference is typically made to animal experiments to the extent they have been carried out. The manufacturer is obligated to update these information with regard to ongoing collection or publication of knowledge. The manufacturer’s interest in relation to use during pregnancy is clearly of defensive character, and the motivation to classify a drug as usable during pregnancy is thus almost non-existing, primarily due to medico legal considerations (135, 136).

Since 2009, an EMA (European Medicines Agency) guideline specifically in this area has existed, which describes the requirements which must be met in order for a given drug to have added specific recommendations during pregnancy (137, 138). The proposed statistical estimates with associated proposal(s) for recommendation text are rather conservative:

i) More than 300 pregnant women without signs of excess incidence of undesired foetal impact must be examined to eliminate that the risk actually has increased by a factor 10. Recommendation text: ‘The risk of malformations in humans is unlikely, but the level of evidence is low’.

ii) More than 1000 pregnant women without signs of excess incidence of undesired foetal impact must be examined to eliminate that the risk actually has increased by a factor 2. Recommendation text: ‘The risk of malformations in humans is unlikely, the level of evidence is high’.

The problem is, of course, the interpretation of this type of data, where the producer’s interest is extraordinarily conservative, which is not necessarily identical with the patient’s and the unborn child’s best interests. In addition, there is still not always consistency in the summaries of the product characteristics for the same active ingredients. For example, SPC for two different citalopram products:

Not recommended for pregnant women, as experience with regard to the use of citalopram for pregnant women is insufficient (140).
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citalopram in the first trimester exist. However, the studies cannot demonstrate an increased general risk of undesired foetal impact besides neonatal symptoms and PPHN in newborns (38–40, 141).

Counselling possibilities. At psychiatric hospitals in Denmark, there are often opportunities for advice on psychopharmacological treatment of pregnant and breast-feeding women. Other possibilities are departments of clinical pharmacology, where you can obtain further information. Many obstetric wards have special offers for pregnant women, where advice and guidance can also be obtained. It is important that fertile women with a psychiatric disease are advised before pregnancy if psychotropic drugs are needed during pregnancy. Valproate and carbamazepine should be avoided if possible for fertile women. If antipsychotics are needed, olanzapine is primarily recommended based on the amount of safety data, but risperidone, quetiapine and clozapine can be used.

Declaration of interest

Dr Erik Roj Larsen, Dr Poul Videbech, Dr Hans Eyvind Dahl Knadsen, Dr Jesper Fenger Gron, Dr Lars Henning Pedersen, Dr Vibeke Johansen Linde and student Lykke Skaarup have no competing interests to report. Rie Lambek Mikkelsen has taught for the following companies: AbbVie A/S, Otsuka Pharma Scandinavia AB, Novartis Healthcare A/S, Lundbeck Pharma A/S and AstraZeneca A/S. René Ernst Nielsen has received teaching fee from Bristol-Myers Squibb, Astra Zeneca, Janssen & Cilag, Servier, Otsuka Pharmaceuticals and Eli Lilly, and has been a member of Advisory Boards for Astra Zeneca, Lundbeck, Otsuka Pharmaceuticals, Takeda, Eli Lilly and Medivir. Per Damkier has served as expert witness for Accord Healthcare Ltd in a Norwegian law suit concerning patent validity for an extended release formulation of ‘Quetiapine’.

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