ACTA UNIVERSITATIS LODZIENSIS
FOLIA PSYCHOLOGICA 10, 2006

CORNELIA THIELS
Department of Social Studies
University of Applied Sciences Bielefeld

PSYCHOACTIVE DRUGS DURING PREGNANCY AND BREAST-FEEDING

INTRODUCTION

Only about 50% of pregnancies are planned (Yonkers et al., 2004). The neural tube closes at the end of the 1st month. Thus, for women with childbearing potential drugs should be prescribed only if necessary. This is true particularly for pregnant and breastfeeding patients. Also, it is advisable to carry out a pregnancy test before the initiation of pharmacotherapy. The woman has to be informed about the necessity of contraception during the period of drug treatment and of family planning that allows stepwise withdrawal of medication at least for the first trimester of pregnancy if possible. This could reduce the incidence of congenital malformations (Yonkers et al., 2004). During treatment with anticonvulsive drugs (which are used as mood stabilizers) hormonal contraceptives may not work as they are more rapidly metabolized due to enzyme induction by the psychoactive medication.

During the second and third trimester there is a risk of minor malformations (craniofacial anomalies), behavioural effects, low birth weight, and preterm delivery (Yonkers et al., 2004). During the last trimester, especially the perinatal period and while breast feeding only essential drugs should be prescribed in order to decrease the risk of toxicity both in the short and in the long term and of withdrawal symptoms. This review aims to help those who treat women with childbearing potential and in particular pregnant and breast feeding women with psychiatric disorders.

METHOD

Medline and hand searches were carried out repeatedly since the late 1970 (Thiels, 1980, 1987, 1992, 1996). The following key words have been used: pregnancy, breast feeding, antidepressant, mood stabilizer, lithium, carbamazepine, valproate, selective serotonin reuptake inhibitor (SSRI), neuroleptic, antipsychotic, psychoactive drug. There is a wealth of reviews some of which are often here due to space restraints quoted rather than all original papers.

RESULTS

Methodological considerations

Studying the risk of psychoactive drugs during pregnancy and breast feeding is burdened with major methodological problems (Thiels, 1980, 1987, 1992). The variety of substances results in small numbers for each one during pregnancy or breast-feeding in epidemiological surveys. Thus, differences in the rate of malformations usually do not exceed the normal annual variation.

Even if the number of pregnant or breast-feeding women taking one particular drug is high enough for an epidemiological approach, it is unlikely to be the same dosage for the same duration at the same stage of pregnancy in all cases or statistically sufficiently large groups. Also, the various indications for psychoactive drug use (e.g. anticonvulsants as mood stabilizers or antiepileptic drugs) lead to largely different dosages (e.g. neuroleptics against schizophrenic and affective psychoses as well as against nausea). In addition, different illnesses necessitating drug treatment may carry or indicate different risks for the child (benzodiazepines against anxiety and miscarriage). When more than one potentially teratogenic or toxic drug is ingested, attribution of harm is difficult if not impossible. Outside drug trials mono-therapy is rather the exception than the rule. In addition, women who take psychoactive drugs may also have a less healthy life style than those of the control group and neglect antenatal care.

Animal studies may warn us of possible safety concerns but can not reassure us that a particular drug is safe in humans. Because of ethical concerns expecting or breast-feeding mothers are not included in randomised controlled trials. Therefore, doses vary even in prospective studies. However, prospective studies are clearly superior to retrospective ones. Information centres where pregnant women can seek advice and their children be

followed up are a useful way to recruit prospective samples (Jacobson et al., 1992). Standardized documentation of variables of interest can be ensured and the pitfall of biased remembering avoided. However, substances like alcohol and tobacco are often consumed by pregnant women – probably more so by those with suffering from mental disorders – but not always admitted to because of their well known harm to the unborn child (Armstrong, 1992; Butler, Goldstein, 1973; Chasnosnoff, 1991; Fingerhut et al., 1990; Garn et al., 1981; Löser, 1982; Siedentopf et al., 2004). In case registers and even more so in case reports malformations and intoxications are likely to be overrepresented.

General considerations

During the treatment of pregnant or breast-feeding patients, the aim is to balance cost vs. benefit for both woman and child. The latter may not only be affected by drugs ingested by the mother but also by her insufficiently treated mental illness. Psychiatric disorders can lead to neglecting antenatal care, prenatal vitamin regime, and proper nutrition, as well as to (increased) smoking and alcohol consumption (Yonkers et al., 2004), risky sexual behaviour and dangerous driving during mania, and suicide attempts. After delivery infanticide, overt child neglect due to serious mental illness and subtler forms of inappropriate response to the infant during postnatal depression should be prevented.

Organ dysgenesis is the main concern in choosing a psychoactive agent for a woman who may become pregnant or during the first trimester. Later **intrauterine growth effects** and **neurobehavioural teratogenicity** have to be considered. In order to avoid **perinatal effects due to intoxication and/or withdrawal** the dose should be reduced during the last trimester if possible – especially during the last two weeks before delivery. In any case, only psychoactive drugs with proven efficacy and known risks should be prescribed in the lowest dose of sufficient effect (Yonkers et al., 2004). Even if a combination of psychoactive drugs is necessary for the treatment of severe mental illness during the first trimester, termination of pregnancy is rarely indicated (Schaefer, Koch, 1998) and certainly not without prenatal diagnosis of major malformation.

Alternatives to drug treatment

Cognitive, cognitive behaviour, interpersonal and **supportive psychotherapies** are effective at least for mild and moderate depression. As an alternative to drug treatment for pregnant women, **bright light therapy**

with 7000 lux has been shown to have an effect size similar to that in antidepressant drug trials (Epperson et al., 2004). **Electroconvulsive therapy** has also been recommended as an alternative to drug treatment during pregnancy and treatment guidelines provided for this special situation (Yonkers et al., 2004). For bipolar patients relapse prevention by structured daily activities to reduce mood lability and sleep deprivation may help too when reducing and/or changing drug treatment (Yonkers et al., 2004).

Psychological therapies for postnatal depression carried out **by experienced psychotherapists, midwives, nurses, health visitors or lay councillors** proved to be beneficial in nearly all of 15 randomized controlled studies (Brocking-ton, 2004). **Involving the patient's partner** seems advantageous (Gjer-dingen, 2003).

Bipolar disorder

Unlike schizophrenia, manic-depressive illness does not seem to reduce fertility. If anything, manic women are rather more than less likely than mentally healthy ones to engage in sexual intercourse without contraception. In addition, the rate of relapse is high after discontinuation of pharmacologic treatment, especially if discontinuation occurs abruptly (Yonkers et al., 2004). Thus, starting women with childbearing potential on this mood stabilizer should be considered very carefully. If a pregnancy is planned the replacement of lithium with a safer drug might be an option for selected patients but only in specialist care (Yonkers et al., 2004). Tapering off has to be slow.

Antidepressants

Tricyclic antidepressants (TAs) do not confer a risk of **organ dysgenesis** as shown in animal and large epidemiological studies (Thiels, 1980, 1987, 1992, 1996). They are therefore definitively safer for the unborn child than lithium during the first trimester of pregnancy. Monoamine oxidase inhibitors (MOIs) must be avoided (Altshuler et al., 1996).

Fluoxetine teratogenecity has been investigated in at least five studies four of which are prospective and controlled. The rate of miscarriages may be increased (Arnon et al., 2000) but not that of malformations (Arnon et al., 2000; Suri et al., 2004).

Antipsychotic drugs

Haloperidol is unlikely to cause organ dysgenesis according to large case series, but there is a **risk of neonatal extra-pyramidal and withdrawal symptoms** (Yonkers at al., 2004).

Teratogenesis after prenatal exposure to **low-potency neuroleptic drugs** seems to be slightly increased with an odds ratio of 1.21. This has been calculated on the basis of three prospective and one retrospective study and a reanalysis of the prospective studies. The number of live births included is 74 337, 71 746 of them were not exposed to teratogenes, 2591 were exposed. The follow-up period was one day through 5 years (Altshuler et al., 1996). As one would expect considering the high numbers, some drugs were prescribed as antinauseants, i.e. very likely in lower than antipsychotic doses and for a shorter period of time. Also, sickness due to pregnancy has different implications regarding both genetic risks and unfavourable rearing conditions. In one study, the rate of malformations in children born to women with psychosis who took chlorpromazine throughout pregnancy was similar to unexposed offspring of psychotic women but about twice the rate in the general population (Sobel, 1960).

No increase in structural teratogenicity has been reported so far and nothing on neonatal toxicity. However, olanzapine has been associated with weight gain and insulin resistance during pregnancy, gestational diabetes and preeclampsia, and no data exist on neonatal toxicity (Yonkers et al., 2004).

Mood stabilizers

In 1970, concern arose about **organ dysgenesis**, notably Ebstein's anomaly, usually a very rare cardiovascular malformation which was reported relatively frequently to The Register of Lithium Babies (Thiels, 1980, 1987, 1992, 1996). The prevalence of congenital heart defects is 5–8 per 1000 live births, making them the most frequent of severe congenital malformations (Smrcek et al., 2004). Ebsteins anomaly occurs in 0.5% of patients with congenital heart disease (Chaoui et al., 1990). Newer studies showed no increase in risk of Ebstein anomaly in case of lithium exposition during pregnancy (Tschudin, Lapaire, 2005). The difference to earlier reports is usually attributed to methodological advances, i.e. prospective studies rather than case registers or case reports. A real decrease of the malformation rate due to lower lithium levels in the past two decades or so compared to the 1960s and '70s is conceivable too.

Carbamazepine and valproic acid are **known teratogenes** (Wide et al., 2004) and are associated with a greater risk of neural tube defects (spina bifida, anencephaly) than lithium. Exposure to these anticonvulsants is also associated with craniofacial anomalies, growth retardation, microcephaly, heart defects, and miscarriage or stillbirth (Yonkers et al., 2004). Thus, it should be prescribed only to **lithium non-responding** women of

childbearing age especially when pregnancy is planned or during the first trimester. If these anticonvulsive drugs are the only option for the prevention of relapse into bipolar disorder 3–4 mg folate/day from four weeks before pregnancy, i.e. when conception is planned until the end of first trimester are recommended for the prevention of spina bifida. It can be reliably diagnosed by fetal ultrasonography at weeks 16–19 (Altshuler et al., 1996; Burt, Rasgon, 2004).

If *lithium* seems necessary during the whole pregnancy, the lithium level should be kept as low as known to be effective for relapse prevention in this particular patient. The lithium level has to be monitored once a month during the first half of pregnancy, once weekly until after delivery and closely during delivery (Yonkers et al., 2004). The lithium dose should be tapered by 25–30% just before delivery as the lithium level may rise to toxic levels otherwise. Fetal cardiac ultrasonography at weeks 16–18 and echocardiography will reassure the patient in most cases that her baby is likely to have no cardiac anomaly (Yonkers et al., 2004). Or preparations can be made well ahead of time for a paediatric cardiologist to attend as early as possible.

In a prospective study, the birth **weight of lithium exposed infants** was **significantly higher** compared to controls in spite of equal duration of gestation and a significantly higher percentage of smokers in the lithium group (Jacobson et al., 1992). This could be due to the influence of lithium on glucose metabolism (Thiels, 1996).

After **late pregnancy exposure to antidepressants** an increased risk was found for preterm birth (odds ration [OR], 1.96) and low birth weight (OR, 1.98) (Källén, 2004). However, a highly significant increase in gestational week-specific birth weight was seen in all singleton infants. There was an increased risk of a low Apgar score (OR, 2.33), respiratory distress (OR, 2.21), neonatal convulsions (OR, 1.90), and hypoglycaemia (OR, 1.62), the latter only after exposure to TAs. No difference between paroxetine and other SSRIs was found. The information had been prospectively recorded in antenatal care records of 997 infants (987 mothers, 395 exposed to tricyclic antidepressants [TAs], 558 to SSRIs) (Källén, 2004).

Newborns whose mothers took tricyclic antidepressants until delivery or not long before have also been reported to suffer hypothermia, lethargy, cyanosis, respiratory acidosis, hypertonia and hypotonia, feeding difficulties, functional bowel obstruction, urinary retention, jitteriness, irritability, convulsions, tachycardia, tachypnoea, and sweating (Thiels, 1987, 1992; Altshuler et al., 1996).

Third trimester fluoxetine exposure had a significantly higher risk of premature delivery, special care nursery admission, poor neonatal adaptation, lower birth weight, lower and shorter birth length, in a study not controlled

for depression (see review by Arnon et al., 2000). When 28 newborns exposed to fluoxetine were compared prospectively to 18 unexposed controls of mothers who had been depressed during pregnancy and 16 unexposed controls of healthy mothers, no significant differences were found regarding gestational age, birth weight, Apgar score, and admission to the neonatal intensive care unit. None of the mothers smoked, used alcohol or other drugs (Suri et al., 2004). The main limitation of this otherwise methodologically rigorous study is the small number of participants, which is possible to lead to false negative results.

Several case reports of possible adverse perinatal effects after SSRI (SSRI) are published. Jitteriness and hypertonia were displayed by two infants after fluoxetine exposure and poor neonatal adaptation with jitteriness, increased respiratory rate and tremors after 30 mg paroxetine from the sixth month of pregnancy (Arnon et al., 2000). Also after paroxetine use two intoxications have been reported with abnormal electroencephalograms in both cases (Herbst, Gortner, 2003; Morag et al., 2004). Lethargy, no crying, and no response to tactile stimulation were displayed by an infant born at term (Morag et al., 2004), and a girl born at 37 weeks of gestation presented hyponea, bradycardia, and decreased muscular tone 12 hours after birth (Herbst, Gortner, 2003). SSRI's are also associated with agitation and tachycardia in the newborn (Altshuler et al., 1996). Mean umbilical cord to maternal serum ratios were significantly lower for sertraline than fluoxetine, suggesting lower fetal exposure to the former medication near delivery. Maternal doses predicted umbilical concentrations of both the drugs (Hendrick et al., 2003).

Neuroleptic drugs during late pregnancy may be followed by tremor, hypertonicity, abnormal movements, jaundice, constipation, difficulty with oral feeding, and motor restlessness (Altshuler et al., 1996; Thiels, 1987). In an infant exposed to haloperidol irritability, tongue thrusting with feeding difficulty, abnormal hand posturing, and tremor of all extremities lasting six months, have been observed (Yonkers et al., 2004). Concomitant treatment with anticholinergic and antihistaminic drugs may play a part in producing these symptoms (Yonkers et al., 2004).

Babies exposed to **lithium around birth** may show hypotonicity and cyanosis. Cases of neonatal hypothyroidism and nephrogenic diabetes insipidus have also been reported (Yonkers et al., 2004).

The **development after intra-uterine exposure to antidepressant drugs** was compared in 80 children exposed prenatally to TCAs, 55 children whose mothers took Fluoxetine while pregnant, and 84 children without the ingestion of a known teratogen during gestation. At birth, there were no differences in gestational age, weight, body length, and head circumference. At 16–86 months, no differences were found in IQ using the Bayley Scales

of Infant Development or McCarthy Scales of Children's abilities nor in temperament, mood, arousability, activity level, distractibility or behaviour problems. Language development was similar for the three groups with the Fluoxetine group achieving rather worse results on the Reynell Developmental Language Scales (Nulman et al., 1997).

Intelligence quotient was similar in 28,358 children at the age of four years, regardless of whether they were exposed to phenotiazines before birth or not (Slone et al., 1977).

Based on a case register, no more physical and psychological problems were found in 60 school children born without malformations after exposure to *lithium*, compared to their unexposed siblings (Schou, 1976).

Unipolar depression, schizophrenia and schizoaffective disorders

These mental illnesses will not be considered separately, as the compounds for their treatment have been discussed above as alternatives to lithium for bipolar disorder.

Anxiety and Obsessive compulsive disorders can be treated successfully using a behavioural or cognitive behavioural approach. A potential problem with these treatments, i.e. lack of compliance, should be greatly reduced during pregnancy if the advantage for the unborn child of avoiding exposure to psychoactive agents is explained to the mother. As women are more motivated even to give up smoking during gestation than at other times in their lives the choice of a drug free treatment should not pose insurmountable problems. Thus, *minor tranquilizers* will not be discussed here. Reviews are provided by C. Thiels (1980, 1982, 1992, 1996) and K. A. Yonkers et al., (2004).

Insomnia as an independent disorder is amenable to drug free treatments too – sleep hygiene and behaviour therapy (Thiels, 2003). If the sleeping problem is a symptom of an affective or psychotic disorder it will be treated in the context of these illnesses for which pharmacotherapy has been discussed above and will have an effect on insomnia too.

Postpartum psychopathology and postpartum prophylaxis

Within the first six months after delivery 5–20% of mothers experience depression and 0.1–0.2% – psychoses. The risk is 100-fold for women with bipolar disorder compared to mothers with no history for postpartum psychosis (Chaudron, Jefferson, 2000). 40% of women with bipolar disorder experience postpartum mania or depression. Each postpartum mania or depression increases risk of future postpartum episode. Postpartum pro-

phylaxis with mood stabilizers decreases the rate of recurrence to 10%. The negative effects of depressed mothers on their infants are well documented (Chaudron, Jefferson, 2000).

Advantages of breast feeding for the mother are faster postpartum weight loss, decreased blood loss due to lactation amenorrhea, a decreased risk of ovarian and breast cancer, an increased intimacy with her infant, increased self-esteem and assertiveness (which depressed women are lacking) and financial savings (Chaudron, Jefferson, 2000). **Breast milk** is the **ultimate nutrition** for the baby because of the unique protein and fat composition. In addition, growth factors promote the development of the gastrointestinal tract. Enzymes facilitate the digestion. Breast milk contains immunoprotective components, bioactive substances such as hormones, enzymes, and live cells as well as vitamins, essential minerals, trace elements (Chaudron, Jefferson, 2000). Lower mortality rates from sudden infant death and necrotizing enterocolitis have been reported for breastfed infants (Chaudron, Jefferson, 2000). Also, they have decreased risks for respiratory infections, gastroenteritis, otitis media, allergies and type I diabetes (Chaudron, Jefferson, 2000).

The infant's ability to absorb, detoxify, and excrete drugs depends on the maturity of renal and liver functions, medical problems and other medications the infant receives (Chaudron, Jefferson, 2000). The ratio of milk to mother's serum drug level is not constant, but depends on dose strength, duration of dosing, variations in drug disposition, diseases, and drug interactions (Chaudron, Jefferson, 2000). After medication during the final weeks of pregnancy breast milk must be pumped and dumped for 1–2 days in order to avoid additive drug exposure via colostrums which contain higher drug levels than mature milk (Chaudron, Jefferson, 2000).

Lithium and breast-feeding

Lithium is eliminated via renal excretion. Its half-life in adults lasts about 24h. As the infant's excretory systems are still immature, attention has to be paid to its increased sensitivity to alterations in fluid and electrolyte balance when exposed to lithium (Chaudron, Jefferson, 2000).

The American Academy of Pediatrics recommends caution when women who take lithium nurse (Yonkers et al., 2004). Breast-milk contains about 40% (24–72%) of the mothers' serum concentration (Chaudron, Jefferson, 2000). The infants' serum concentration ranges from 5–200% of the mothers' serum concentration (Chaudron, Jefferson, 2000).

However, to my knowledge only three case reports of nursing infants with adverse events attributed to lithium have been published (Thiels, 1987, 1992), one with the recommendation to breast feed nevertheless (Thiels, 1992), and all of them from a period when patients were treated with higher lithium levels than today.

Thus, **the mother and her supporters should be informed** about the pros and cons of breast-feeding while taking lithium and of the signs of lithium toxicity in the infant. It should be clear to everyone involved that to stop lithium treatment is no option as a manic or depressed mother is worse for the infant than being bottle-fed. The risks of infant dehydration and its effects on lithium levels have to be explained to the mother and her supporters, and formula supplements should be used partially or totally during the infant's illness or dehydration (Chaudron, Jefferson, 2000; Thiels, Ch. personal communication 2003). If **lithium toxicity** is suspected, infant and maternal lithium levels have to be obtained and breast-feeding might be suspended, at least temporarily (Chaudron, Jefferson, 2000).

However, the **compliance** with such recommendations may be low. According to questionnaires filled in by the mothers themselves, more than two fifth failed to stick to the following counsel – only 20 mg paroxetine in a single dose after the last feed of the day, avoidance of certain drugs, and close medical follow-up of the infant (Merlob et al., 2004).

Infants nursed by a woman on valproic acid are exposed to the lowest dose of psychoactive drug, followed by carbamazepine. Both are compatible with breast-feeding according to the American Academy of Pediatrics, in spite of limited information (Yoshida et al., 1999) and adverse effects associated with carbamazepine. There are concerns regarding nursing while taking lamotrigine.

Antidepressants and breast-feeding

Amitriptyline, nortriptyline, desimipramine, clomipramine, dothiepin and sertraline were not found in quantifiable amounts in breast-fed infants, and no **adverse events were reported** by K. L. Wisner et al., (1996). However, K. Yoshida et al., (1997b) detected imipramine, amitriptyline, clomipramine, dothiepine in the range of 0.5 mg/ml (imipramine) to 7.5 mg/ml (amitriptyline). But, again the 10 breast-fed babies did not show any gross deficits on the Bayley Scales (MDI and PDI) and the Amiel-Tison neurological assessment attributable to tricyclics when studied up to 4 times between the ages of 1–30 months. They did not differ during the ages 1–11 months from the 15 bottle-fed infants followed-up for only one year. The risk for adverse effects of tricyclic antidepressants passed on via breast-milk

to **infants older than 10 weeks** is considered to be low and there is no evidence of accumulation (Wisner et al., 1996). If the infants is healthy it is likely that the benefits of breast-feeding outweigh potential hazards, if their mothers take established tricyclic drugs at recommended dose levels (Yoshida et al., 1999).

Much less is known about the safety of SSRI which enter breast-milk (Yoshida et al., 1999). *Adverse effects* have been noted in some young infants whose mothers had been treated with **doxepin, fluoxetine, citalopram**, or **nefazodon** during breastfeeding (Wisner et al., 1996; Gjerdingen, 2003), but not in four others exposed to fluoxetine and nurfluoxetine via 39–177 mg/ml breast-milk (Yoshida et al., 1998a) and two nursed by mothers treated with fluvoxamine (Yoshida et al., 1997a).

Except for irritability in one baby, no adverse paroxetine effects were reported in a prospective cohort study (Merlob et al., 2004). No significant differences were detected in mean weight at ages of 3, 6, and 12 months between the infants of 27 mothers who took **paroxetine** for at least two weeks while breast-feeding and those of 19 mothers who neither took this medication nor breast-fed, and 17 mothers who breast-fed but did not take any drugs (Merlob et al., 2004). The usual developmental milestones were reached in all groups. The mothers completed a detailed outcome questionnaire and paediatricians and nurses at well-baby clinics and paediatric services completed routine follow-up forms.

Breast-feeding and antipsychotic drugs

In the majority of 28 babies exposed to **first-generation neuroleptic** drugs via breast-milk, no adverse events were observed (Yonkers et al., 2004). However, during treatment with **chlorpromazine**, breast-feeding should be avoided. Infants are reported to be sleepy and lethargic with 96 mg/l milk. In addition, there is a risk of hypothermia, other CNS- and haematological side effects. Also, pharmacokinetic information is minimal so far (Winans et al., 2001). Little is known about risks associated with phenotiazines and butyrophenones, which both enter breast-milk (Yoshida et al., 1999). Three babies nursed by their mothers, who were treated with the **combination of high doses of chlorpromazine and haloperidol** showed substantial falls in the Bayley Scale scores for infants by 12–18 months but not four exposed to haloperidol only and one ingesting chlorpromazine only via breast-milk (Yoshida et al., 1998a). All infants were normal at 1–18 months on the Amiel-Tison neurological test.

Breast-feeding should be avoided while taking **olanzapine**. Twenty-seven cases have been reported by Eli Lilly, two of them published, amongst the

former four cases of adverse events. The first baby displayed jaundice, cardiomegaly, heart murmur, the second one – tremor, poor sucking, lethargy, the third one – a protruding tongue, and the fourth baby – skin rash, diarrhoea, and sleeping problems (Gardiner et al., 2003).

Breast-feeding is contraindicated during treatment with **clozapine** because of the increased risk of agranulocytosis and seizures compared to conventional antipsychotic drugs. The milk/plasma-Ratio is 2.5 (Winans, 2001).

In any case, the **best drug for mother should be chosen** – regardless of breast-feeding status. She has to be informed about the risk of nursing while taking medication, about the benefits of breast-feeding, and about the risks of not taking medication. She should than decide herself about breast-feeding (Chaudron, Jefferson, 2000).

Desiderata

Systematic research on the short and long term effects of psychoactive drugs after prenatal exposure and ingestion via breast-milk is urgently needed in the times of increasing prescribing of psychoactive drugs, in spite of a lack of evidence for that, this is for the benefit of the population served (Brugha et al., 2004). Such studies should be carried out with appropriate controls regarding the severity of psychiatric disorder(s), the extent and duration of exposure as well as nicotine, alcohol, and illegal drug use.

CONCLUSIONS

For women taking psychoactive drugs during their reproductive years, contraception is advisable. When pregnancy is planned and during the first trimester of it, lithium, carbamazepine, and valproate should be avoided if possible. Conventional neuroleptics and tricyclics might be an alternative. The teratogenicity of atypical antipsychotics is largely unknown. In order to avoid side effects in the newborn, antidepressants and neuroleptics should not be given in high doses during the last two weeks before delivery.

In order to avoid additive drug exposure via colostrum it must be pumped and dumped for 1–2 days if the newborn has been exposed to psychoactive drugs shortly before birth (Chaudron, Jefferson, 2000). Caution is warranted during breast-feeding while taking lithium. If the mother responds to medication not contraindicated during breast-feeding and wants to nurse, she should take her medication immediately after breastfeeding. All those caring for the baby have to be informed about signs of toxicity in the nursed infant. Formula supplements should be used partially or totally

during the infant's illness or dehydration. If toxicity is suspected infant and maternal drug levels have to be obtained and breast-feeding should be suspended.

For women of childbearing age, and especially during pregnancy and breast feeding, only few – if any – psychoactive drugs at a time and only those with proven efficacy and known risks should be prescribed in the lowest dose of sufficient effect. Partly because older drugs are better known than newer ones, conventional neuroleptic drugs are rather preferable to atypical antipsychotics and tricyclic antidepressants to SSRIs.

The author thanks Dr. Almut Nagel-Brotzler for her contribution of gynaecological expertise and several references.

REFERENCES

Altshuler L. L., Cohen L., Szuba M. P., Burt V. K., Gitlin M., Mintz J. (1996), *Pharmacologic Management of Psychiatric Illness during Pregnancy: Dilemmas and Guidelines*, ''American Journal of Psychiatry'', **153**, 592–606

Armstrong B. G., McDonald A. D., Sloan M. (1992), *Cigarette, alcohol and coffee consumption and spontaneous abortion*, ''American Journal of Public Health'', **82**, 85–87

Arnon J., Shechtman S., Ornoy A. (2000), *The Use of Psychiatric Drugs in Pregnancy and Lactation*, ''The Israel Journal of Psychiatry and Related Sciences'', **37**, 205–222

Brockington I. (2004), *Diagnosis and Management of Post-Partum Disorders: A Review*, ''World Psychiatry'', **3**, 89–95

Brugha T. S., Bebbington P. E., Singleton N., Melzer R., Jenkins R., Lewis G., Farrell M., Lee A., Meltzer H. (2004), *Trends in Service use and Treatment for mental disorders in Adults throughout Great Britain*, ''British Journal of Psychiatry'', **185**, 378–384

Burt V. K., Rasgon N. (2004), *Special Considerations in Treating Bipolar Disorder in Women*, ''Bipolar Disorders'', **6**, 2–13

Butler N. R., Goldstein H. (1973), *Smoking in pregnancy and subsequent child development*, ''British Medical Journal'', **4**, 573–575

Chaoui R., Bollmann R., Hoffmann H., Zienert A., Bartho S. (1990), *Eine Ebstein-Anomalie als seltene Ursache eines nicht immunologischen Hydrops fetalis (NIHF): Pränatale Diagnose mittels Doppler-Echocardiographie*, ''Klinische Pädiatrie'', **202**, 173–175

Chasnosnoff I. J. (1991), *Drugs, alcohol and the neonate: pay now or pay later*, ''Journal of the American Medical Association'', **266**, 1567–1568

Chaudron L. H., Jefferson J. W. (2000), *Mood Stabilizers during Breastfeeding: A review*, ''Journal of Clinical Psychiatry'', **61**, 79–90

Epperson C. N., Terman M., Terman J. S., Hanusa B. H., Oren D. A., Peindl K. S., Wisner K. L. (2004), *Randomized Clinical Trial of Bright Light Therapy for Antepartum Depression: Preliminary Findings*, ''Journal of Clinical Psychiatry'', **65**, 421–425

Fingerhut L. A., Kleinmann, J. C., Kendrick J. S. (1990), *Smoking before, during and after pregnancy*, ''American Journal of Public Health'', **80**, 541–544

Gardiner S. J., Kristensen J. H., Begg E. J., Hackett L. P., Wilson D. A., Ilett K. F., Kohan R., Rampono J. (2003), *Transfer of Olanzapine into Breast Milk,*

Calculation of Infant Drug Dose, and Effect on Breast-Fed Infants, ''American Journal of Psychiatry'', **160**, 1428–1431

Garn S. M., Johnston M., Ridella S. A., Petzold A. S. (1981), *Effect of maternal cigarette smoking on Apgar scores*, ''American Journal of Diseases in Children'', **135**, 503–506

Gjerdingen D. (2003), *The Effectiveness of Various Postpartum Depression Treatments and the Impact of Antidepressant Drugs on Nursing Infants*, ''The Journal of the American Board of Family Practice'', **16**, 372–382

Hendrick V., Stove Z. N., Altshuler L. L., Hwang M. S., Lee E., Haynes D. (2003), *Placental Passage of Antidepressant Medication*, ''American Journal of Psychiatry'', **160**, 993–996

Herbst F., Gortner L. (2003), *Paroxetin-Entzugs-Syndrom als Differentialdiagnose der akuten neonatalen Enzephalopathie?*, ''Zeitschrift für Geburtsthilfe & Neonatologie'', **207**, 232–234

Jacobson S. J., Jones K., Johnson K., Ceolin L., Kaur P., Sahn D., Donnenfeld A. E., Rieder M., Santelli R., Smythe J., Pastuszak A., Einarson T., Koren G. (1992), *Prospective multicentre study of pregnancy outcome after lithium exposure during first trimester*, ''Lancet'', **339**, 530–533

Källén B. (2004), *Neonate Characteristics after Maternal Use of Antidepressants in Late Pregnancy*, ''Archives of Pediatric and Adolescent Medicine'', **158**, 312–316

Löser H. (1982), *Erkennungsmerkmale der Alkoholembryopathie*, ''Deutsches Ärzteblatt'', **79**, 37, 34–39

Merlob P., Stahl B., Sulkes J. (2004), *Paroxetine during breast-feeding: infant weight gain and maternal adherence to counsel*, ''European Journal of Pediatrics'', **163**, 135–139

Morag I., Batash D., Keidar R., Bulkowstein M., Heyman E. (2004), *Paroxetine Use Throughout Pregnancy: Does It Pose Any Risk To The Neonate?*, ''Journal of Toxicology'', **42**, 97–100

Nulman I., Rovet J., Steward D. E., Wolpin J., Gardner H. A., Theis J. G., Kulin N., Koren G. (1997), *Neurodevelopment of Children Exposed in Utero to Antidepressant Drugs*, ''New England Journal of Medicine'', **336**, 258–262

Schaefer C., Koch I. (1998), *Die Beratung der Schwangeren und Stillenden zum Medikamentenrisiko*, ''Deutsches Ärzteblatt'', **95**, 2637–2642

Schou M. (1976), *What Happened Later to the Lithium Babies? A Follow-Up Study of Children Born Without Malformations*, ''Acta Psychiatrica Scandinavica'', **54**, 193–197

Siedentopf J.-P., Nagel M., Büscher U., Dudenhausen J. W. (2004), *Alkohol konsumierende Schwangere in der Schwangerenberatung*, ''Deutsches Ärzteblatt'', **101**, 2623–2626

Slone D., Siskind V., Heinonen O. P., Monson R. R., Kaufman D. W., Shapiro S. (1977), *Antenatal exposure to the phenothiazines in relation to congenital malformations, perinatal mortality rate, birth weight and intelligence quotient score*, ''American Journal of Obstetrics and Gynecology'', **128**, 486–488

Smrcek J., Krapp M., Axt-Fliedner R., Gembruch U. (2004), *Frühe fetale Echokardiographie*, ''Der Gynäkologe'', **37**, 716–724

Sobel D. (1960), *Fetal Damage Due To ECT, Insulin Coma, Chlorpromazine or Reserpine*, ''Archives of General Psychiatry'', **2**, 606–611

Suri R., Altshuler L., Hendrick V., Rasgon N., Lee E., Mintz J. (2004), *The Impact of Depression and Fluoxetine Treatment on Obstetrical Outcome*, ''Archives of Women's Mental Health'', **7**, 193–200

Thiels C. (1980), *Psychopharmaka in der Schwangerschaft: Eine Übersicht*, ''Psychopharmacopsychiatrie'', **13**, 301–317

Thiels C. (1987), *Pharmacotherapy of Psychiatric Disorder in Pregnancy and during Breastfeeding. A review*, ''Pharmacopsychiat'', **20**, 133–146

Thiels C. (1992), *Psychopharmaka in der Schwangerschaft und Stillzeit*, [in:] P. Riederer, G. Laux, W. Pöldinger (eds.), *Neuro-Psychopharmaka. Volume 1: Allgemeine Grundlagen der Pharmakopsychiatrie*, Springer, Wien–New York, 353–380

Thiels C. (1996), *Psychopharmaka während Schwangerschaft und Stillzeit. Kap. 69*, [in:] V. Faust (ed.), *Psychiatrie – Ein Lehrbuch für Klinik, Praxis und Beratung*, Gustav Fischer, Stuttgart–New York, 783–787

Thiels C. (2003), *Was tun bei Schlafstörungen*, [in:] C. Thiels, *Das Selbsthilfeprogramm bei Depressionen*, Herder, Freiburg, 133–139

Tschudin S., Lapaire O. (2005), *Antidepressiva in der Schwangerschaft*, ''Therapeutische Umschau'', **62**, 17–22

Wide K., Windbladh B., Källén B. (2004), *Major Malformations in Infants Exposed to Antiepileptic Drugs in Utero, with Emphasis on Carbamazepine and Valproicacid: A Nation-Wide, Population-Based Register Study*, ''Acta Pediatrica'', **93**, 174–176

Winans E. A. (2001), *Antidepressant Use during Lactation*, ''Journal of Human Lactation'', **17**, 256–261

Wisner K. L., Perel J. M., Findling R. L. (1996), *Antidepressant Treatment during Breast-Feeding*, ''American Journal of Psychiatry'', **153**, 1132–1137

Yonkers K. A., Wisner K. L., Stowe Z., Leibenluft E., Cohen L., Miller L., Manber R., Viguera A., Suppes T., Altshuler L. (2004), *Management of Bipolar Disorder During Pregnancy and the Postpartum Period*, ''American Journal of Psychiatry'', **161**, 608–620

Yoshida K., Smith B., Kumar R. C. (1997a), *Fluvoxamine in Breast-Milk and Infant Development*, ''British Journal of Clinical Pharmacology'', **44**, 210–211

Yoshida K., Smith B., Craggs M., Kumar R. C. (1997b), *Investigation of pharmacokinetics and of possible adverse effects in infants exposed to tricyclic antidepressants in breast-milk*, ''Journal of Affective Disorders'', **43**, 225–237

Yoshida K., Smith B., Craggs M., Kumar R. C. (1998a), *Fluoxetine in Breast-Milk and Developmental Outcome of Breast-Fed Infants*, ''British Journal of Psychiatry'', **172**, 175–179

Yoshida K., Smith B., Craggs M., Kumar R. C. (1998b), *Neuroleptic Drugs in Breast-Milk: A Study of Pharmacokinetics and of Possible Adverse Effects in Infants*, ''Psychological Medicine'', **28**, 81–91

Yoshida K., Smith B., Kumar R. C. (1999), *Psychotropic Drugs in Mothers' Milk: A Comprehensive Review of Assay Methods, Pharmacokinetics and of Safety of Breast-Feeding*, ''Journal of Pharmacology'', **13**, 64–80

CORNELIA THIELS

ZAŻYWANIE ŚRODKÓW PSYCHOTROPOWYCH W CZASIE CIĄŻY I KARMIENIA PIERSIĄ

Cel. Prezentacja zasad leczenia zaburzeń psychicznych u kobiet w okresie reprodukcyjnym. Metoda. Analiza prac przeglądowych i wyników prowadzonych badań.

Rezultaty. Sole litu, karbamazepina i kwas walproinowy nie powinny być stosowane w pierwszym trymestrze ciąży. Stosunkowo bezpieczne są w tym okresie trójpierścieniowe leki przeciwdepresyjne. Haloperidol również nie wywołuje uszkodzeń płodu. Redukcja dawki pod koniec ciąży pozwoli uniknąć objawów zatrucia i objawów odstawienia u noworodka. U zdrowych

niemowląt korzyści związane z karmieniem piersią wydają się ważniejsze niż możliwe zagrożenie związane z działaniem trójpierścieniowych leków przeciwdepresyjnych, a także z działaniem soli litu. Niewiele wiadomo natomiast o skutkach działania znajdujących się w mleku matki takich środków jak inhibitory zwrotnego wychwytu serotoniny, leki przeciwpsychotyczne czy karbamazepina.

Wnioski. Wskazane jest stosowanie leków o udowodnionej skuteczności i znanych efektach ubocznych (a więc substancji dłużej znanych niż wprowadzonych ostatnio). Zalecana jest terapia jednym lekiem podawanym w najniższych efektywnych dawkach. Psychoterapia i elektrowstrząsy mogą być alternatywą dla leczenia farmakologicznego.

Słowa kluczowe: leki psychotropowe, ciąża, karmienie piersią, leki przeciwdepresyjne, stabilizatory nastroju, leki przeciwpsychotyczne.