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Care of the Pregnant Woman with Mental Illness

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Care of the Pregnant Woman with Mental Illness

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Are Psychotropic Medications Safe to use during Pregnancy and Lactation?

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Psychotropics and Pregnancy

FDA NEWS RELEASE

FOR IMMEDIATE RELEASE
P05-97
December 8, 2005

Media Inquiries:
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888-INFO-FDA

FDA Advising of Risk of Birth Defects with Paxil

Agency Requiring Updated Product Labeling

The Food and Drug Administration today is alerting health care professionals and patients about early results of new studies for Paxil (paroxetine) suggesting that the drug increases the risk for birth defects, particularly heart defects, when women take it during the first three months of pregnancy. Paxil is approved for the treatment of depression and several other psychiatric disorders. FDA is currently gathering additional data and waiting for the final results of the recent studies in order to better understand the higher risk for birth defects that has been seen with Paxil.

FDA is advising health care professionals to discuss the potential risk of birth defects with patients taking Paxil who plan to become pregnant or are in their first three months of pregnancy. Health care professionals should consider discontinuing Paxil (and switching to another antidepressant if indicated) in these patients. In some patients, the benefits of continuing Paxil may be greater than the potential risk to the fetus. FDA is advising health care professionals not to prescribe Paxil in women who are in the first three months of pregnancy or are planning pregnancy, unless other treatment options are not appropriate.

FDA is advising patients that this drug should usually not be taken during pregnancy, but for some women who have already been taking Paxil, the benefits of continuing may be greater than the potential risk to the fetus. Women taking Paxil who are pregnant or plan to become pregnant should talk to their physicians about the potential risks of taking the drug during pregnancy. Women taking Paxil should not stop taking it without first talking with their physician.

The early results of two studies showed that women who took Paxil during the first three months of pregnancy were about one and a half to two times as likely to have a baby with a heart defect as women who received other antidepressants or women in the general population. Most of the heart defects reported in these studies were atrial and ventricular septal defects (holes in the walls of the chambers of the heart). In general, these types of defects range in severity from those that are minor and may resolve without treatment to those that cause serious symptoms and may need to be repaired surgically.

In one of the studies, the risk of heart defects in babies whose mothers had taken Paxil early in pregnancy was about 2 percent, compared to a 1 percent risk in the whole population. In the other study, the risk of heart defects in babies whose mothers had taken Paxil in the first three months of pregnancy was 1.5 percent, compared to 1 percent in babies whose mothers had taken other antidepressants in the first three months of pregnancy.

FDA has asked the manufacturer, Glaxo Smith Kline (GSK), to change the pregnancy category from C to D, a stronger warning. Category D means that studies in pregnant women (controlled or observational) have demonstrated a risk to the fetus. However, the benefits of therapy may outweigh the potential risks to the fetus.

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Original Article

ONLINE FIRST

Antidepressant Use During Pregnancy and Childhood Autism Spectrum Disorders

Lisa A. Croen, PhD; Judith K. Grether, PhD; Cathleen K. Yoshida, MS; Roxana Odouli, MSPH; Victoria Hendrick, MD

Arch Gen Psychiatry. Published online July 4, 2011. doi:10.1001/archgenpsychiatry.2011.73

Context The prevalence of autism spectrum disorders (ASDs) has increased over recent years. Use of antidepressant medications during pregnancy also shows a secular increase in recent decades, prompting concerns that prenatal exposure may contribute to increased risk of ASD.

Objective To systematically evaluate whether prenatal exposure to antidepressant medications is associated with increased risk of ASD.

Design Population-based case-control study. Medical records were used to ascertain case children and control children and to derive prospectively recorded information on mothers' use of antidepressant medications, mental health history of mothers, and demographic and medical covariates.

Setting The Kaiser Permanente Medical Care Program in Northern California.

Participants A total of 298 case children with ASD (and their mothers) and 1507 randomly selected control children (and their mothers) drawn from the membership of the Kaiser Permanente Medical Care Program in Northern California.

Main Outcome Measures ASDs.

Results Prenatal exposure to antidepressant medications was reported for 20 case children (6.7%) and 50 control children (3.3%). In adjusted logistic regression models, we found a 2-fold increased risk of ASD associated with treatment with selective serotonin reuptake inhibitors by the mother during the year before delivery (adjusted odds ratio, 2.2 [95% confidence interval, 1.2-4.3]), with the strongest effect associated with treatment during the first trimester (adjusted odds ratio, 3.8 [95% confidence interval, 1.8-7.8]). No increase in risk was found for mothers with a history of mental health treatment in the absence of prenatal exposure to selective serotonin reuptake inhibitors.

Conclusion Although the number of children exposed prenatally to selective serotonin reuptake inhibitors in this population was low, results suggest that exposure, especially during the first trimester, may modestly increase the risk of ASD. The potential risk associated with exposure must be balanced with the risk to the mother or fetus of untreated mental health disorders. Further studies are needed to replicate and extend these findings.

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Antidepressant use in pregnancy may raise autism risk

Health.com

By **Anne Harding**, Health.com
July 6, 2011 9:22 a.m. EDT

The study is the first to look at the association between the use of antidepressants during pregnancy and the risk of autism.

STORY HIGHLIGHTS

- The study doesn't prove taking SSRIs during pregnancy directly causes autism
- The findings will need to be confirmed in future studies
- Women should not be

(Health.com) -- Children whose mothers take Zoloft, Prozac, or similar antidepressants during pregnancy are twice as likely as other children to have a diagnosis of autism or a related disorder, according to a small new study, the first to examine the relationship between antidepressants and autism risk.

This class of antidepressants, known as selective serotonin reuptake

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Pregnancy

- As per CDC 50% pregnancies in United States are unintended (PRAMS data 2001)
- 80% of pregnant are prescribed meds
- One third take psychotropic's
- Hyper vigilance towards psych meds
  - Ebstein's — 1/1,000 (Normally 1/20,000)
  - Neural tube defects — 1/500 (Normally 1/1,000)
  - PPHN — 1/100 (Normally 1/1,000)
- Psych meds discouraged, esp. by PCP/OBGYN
- Nausea, headaches, infections routinely treated despite limited safety data

FDA category in pregnancy

- A – Well controlled human studies negative
- B - Either animal studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women, or animal studies have shown an adverse effect that was not confirmed in human controlled studies
- C- Animal studies positive, no human data. Benefits may exceed risk
- D- Human studies positive. Benefits may still exceed risk
- E- Contraindicated. Risk clearly outweighs any potential benefit

The Pregnancy and Lactation Labeling Rule (PLLR)

- In December 2014, the FDA published the new The Pregnancy and Lactation Labeling Rule (PLLR) which took effect on June 30, 2015:. This will change the current prescription drug labeling (A, B, C, D and X) to a new system that is intended to help healthcare providers better understand risks and benefits and communicate this to their patients more appropriately. New medications approved after June 2015 will no longer have the old safety categories and all drugs approved after June 30, 2001 have a minimum of 3 years to submit updated information to meet requirements for the PLLR (Mosley et. al. 2015). Critics of the ABCDX labeling system have long pointed out that not all drugs within the same category provide the same risk, and the categories are often misleading especially for medications for which no human data exists.

- The new labeling will include three updated categories:
  - Pregnancy (information regarding pregnancy exposure),
  - Lactation (amount of drug transferred in breast milk and potential effects on the infant), and
  - Females and Males of Reproductive Potential (contraception recommendations and information about infertility).

The Lactation section will include information on how much of the drug is secreted in the breast milk and how this amount compares to blood concentrations and this information will be used to determine how much of the drug is consumed by the infant.

Under each of the above mentioned sections, the general outline for each drug includes whether or not a registry for the drug exists, a general background risk statement, clinical considerations (with prescribing decision making suggestions for providers), and summary of the available data from trials (human and animal data will be presented separately). (Ramoz and Patel-Shori 2014).

Antidepressants use in 1st Trimester

- Sloane Epidemiology Center Birth Defects Study recently confirmed that that the overall risk of having a child affected by SSRI use was only 0.2% (Louik et al., 2007). They did note increased risk of three birth defects with SSRI use in the first trimester: omphalocele and septal defects with Sertraline, and the heart defect right ventricular outflow tract obstruction with Paroxetine. But only 2% to 5% of infants with these defects were exposed to SSRIs.

Antidepressant use in 2nd Trimester

- In 2006 Chambers and colleagues published a study that found a possible association between SSRI exposure after 20 weeks gestation (second half) and persistent pulmonary hypertension of the newborn (PPHN), a serious and rare condition with a baseline rate of 1-2 out of 1,000 live births and mortality rate of 10 % to 20%. This was a retrospective study, but still its findings are concerning.

Chambers CD, Hernandez-Diaz S, Van Marter IJ, et al. SSRI and risk of persistent pulmonary hypertension of the newborn. *N Eng J Med. 2006;354 (6):579-587.*

Antidepressant use in 3rd Trimester

- Using a formal screening tool, one study found that 30 % of newborns exposed to SSRI's in late pregnancy developed neonatal withdrawal symptoms. *
- Discontinuation syndrome includes acrocynaosis, tachypnea, temperature instability, irritability, constant crying, hypo or hypertonia, feeding and sucking problems and elevated drug levels (Oberlander et al., 2004).
- Fortunately, these symptoms are generally mild and self-limiting, last for 24 to 48 hours, and do not require further treatment. Though in some cases hospitalization can be prolonged.

*Levinson-Castiel R, Merlob P, Linder N, Sirota L, Kinger G, Neonatal abstinence syndrome after in utero exposure to SSRI's in term infants

Neonatal SSRI Withdrawal

- **Symptoms** Initial lack of crying
  Increased muscle tonus
  Irritability, jitteriness
  Abnormal breathing pattern
  Disrupted sleep and motor activity

Cause Serotonin over stimulation or withdrawal (may mimic serotonin syndrome)

Treatment Close Observation
Supportive measures

Autism

- Using Kaiser Permanente's patient database, which includes more than 3.2 million people, Croen and her team identified 298 children with an ASD (Autism Spectrum Disorder) who were born between 1995 and mid-1999, and matched them with 1,507 children without autism who were roughly the same age and were born in the same hospitals
- 6.7 % of the children with an ASD (20 out of 298) were exposed to SSRIs in the womb, compared with 3.3% (50 out of 1507) of the control children. After taking into account other factors that could affect both autism risk and SSRI use (such as the mother's age, ethnicity, and history of depression or other mental illness), the researchers found that any exposure to the drugs in the womb increased the risk of ASD diagnosis 2.2-fold, while first-trimester exposure increased the risk 3.8-fold

Archives of Gen Psychiatry July 4 2011

Long Term Neurobehavioral Effects

- In a cohort of children 4-5 years of age exposed in utero to SSRI's levels of internalizing and externalizing behavior did not differ significantly between children who were (n=22) or were not (n=14) exposed prenatally to SSRI's.*
- In another study , Nulman and colleagues compared mother-child pairs exposed to TCA's (n=46), or fluoxetine (n=40) to a non depressed group (n=46). Children between 15 and 71 months of age were assessed and compared in terms of IQ, language, behavior, temperament, with adjustment to severity of maternal depression, maternal IQ, SES, maternal smoking, and alcohol history. No differences were found. +
- In fact, it was exposure to maternal depression which was associated with less language and cognitive achievement.

*. Misri S, Reebye P, Kendrick K, et al. Internalizing behavior in 4 yr old children exposed in utero to psychotropic medications. *Am. J. Psychiatry . 2006; 163(6): 1026-1032.*

*. Oberlander TF, Reebye P. Misri S, Papsdorf M, Kim J, Grunau RE, Externalizing and attentional behaviors in children of depressed mothers treated with a SSRI during pregnancy.*Arxh. Ped. Adol. Med. 2007; 161 (1):22-29*

+. Nulman I, Rovet J, Stewart DE, et al, Child development following exposure to TCA's or fluoxetine throughout fetal life: a prospective, controlled study. *Am J Psychiatry. 2002;159 (11):1889-1895.*

Paroxetine-Category D

- Risks: Has been associated with fetal heart defects when taken during the first three months of pregnancy; has been associated with PPHN when taken during the last half of pregnancy; has been associated with anencephaly, craniosynostosis and omphalocele
- Recommendation: Due to higher incidence than some other SSRI, AVOID during pregnancy

Lithium-Category D

- Early reports of 400 fold increase in cardiac malformations
- Now estimated at 1-2/1,000 although questions about study design
- Exposure during 21-56 days may affect cardiac development
- No cardiac risk if used after week 10-12 (as fetal heart is formed by week 12)
- No neurobehavioral effects long term

Lithium: Ebstein's Anomaly

- Malformation of Tricuspid valve and Right Atrium
  - One or two leafs stick to heart wall
  - 20-40% of neonates do not survive the first month
  - Surgical repair
  - 50 % associated with ASD

Valproic acid-Category D

(X for Migraine Prophylaxis)

- Valproic acid has a well established risk of neural tube defects of 1.0% to 5.0%
- Effects are dose dependent
- Facial cleft defects 1/700
- Hypospadias 1/250
- Craniosynostosis 1/2000
- Potential neonatal irritability, feeding difficulties, abnormal tone, liver toxicity, hypoglycemia, and PCOs

GG Briggs Drugs in Pregnancy and Lactation, Willams and wilkins: Philadelphia 2008 pp 1025-1935

Valproic acid: Neural Tube Defects

- Risk occurs up to 8th week
  - In US nearly half of pregnancies unplanned!
  - 1-2% risk of spina bifida
  - 3.8% risk of neural tube defects
- Try to keep dose < 1,000mg/day, level < 70
- Supplement with folate 4-5mg/day does not decrease risk
- Once daily dose can cause unpredictably high peak levels

Valproate and developmental delay

- After 3 years , valproate exposed infants had lower IQ's than those exposed to other AED
- IQ was about 9 point lower
- One third might need additional educational support
- Valproate often associated with
  - Development delay - 20%
  - Mental retardation - 10%

Meador KJ et al, NEJM 360; 1597-1605

Carbamazepine-Category D

- Risk of neural tube defects 0.5-1%
- Facial cleft incidence 0.5%
- Associated with reduced head circumference and birth weight
- No neurodevelopmental delay

GG Briggs Drugs in Pregnancy and Lactation, Willams and wilkins: Philadelphia 2008 pp 1025-1935

Typical Antipsychotics

- Low potency typicals raise risk of congenital anomalies from 2.0 to 2.4 %, but no consistent birth defect (meta analysis by Altshuler et al)
- Haloperidol in a prospective study with 215 pregnancies showed more prematurity and low birth weight

Einarson Curr Women's Health Review, 2010,8

Atypical Antipsychotics

- Cautions needs to be observed for metabolic side effects of atypicals due to wt gain, insulin resistance and increased risk of gestational DM and pre eclampsia.
- The only prospective study by Motherisk in 2005 showed
  - 211 women exposed to atypicals
  - 6 on clozapine, 36 on quetiapine, 49 on risperidone, 60 on olanzapine
  - No significant difference in major malformation or pregnancy outcome
  - Birth weight was low in exposed babies, 10% compared to 2 % in comparison group

McKenna et al, J. Clinical Psychiatry 66; 444-449, 2005

Benzodiazepines- Category D

- Most are category D (clonazepam C/D)
  - Category X
    - Estazolam (ProSom)
    - Flurazepam (Dalmane)
    - Temezepam (Restoril)
    - Triazzolam (Halcion)
    - Quazepam (Doral)

Remember for Pregnancy

- DO NOT USE 5: Paxil, Lithium, Valproic, Benzodiazepines and Carbamazepine
- AVOID MAOI's

Psychotropics and Lactation

Breastfeeding

- WHO (World Health Organization), AAP (American Academy of Pediatrics) , ACOG (American College of Obstetrics and Gynecology) all recommend breast milk exclusively for at least the first 6 months of life and continued breast milk with food through 6-12 months of age.
- Most psychiatric drugs are lipid soluble and pass easily into breast milk.
- Highly protein bound drugs, drugs with large volume of distribution and large molecular weight, make drug poorly lipid soluble and hence the level secreted in breast milk are low
- The most reliable method for measuring infant drug exposure is by measuring the drug level in infant's serum
- Hind milk, or second half of feeding is likely to have a higher concentration of maternal medication

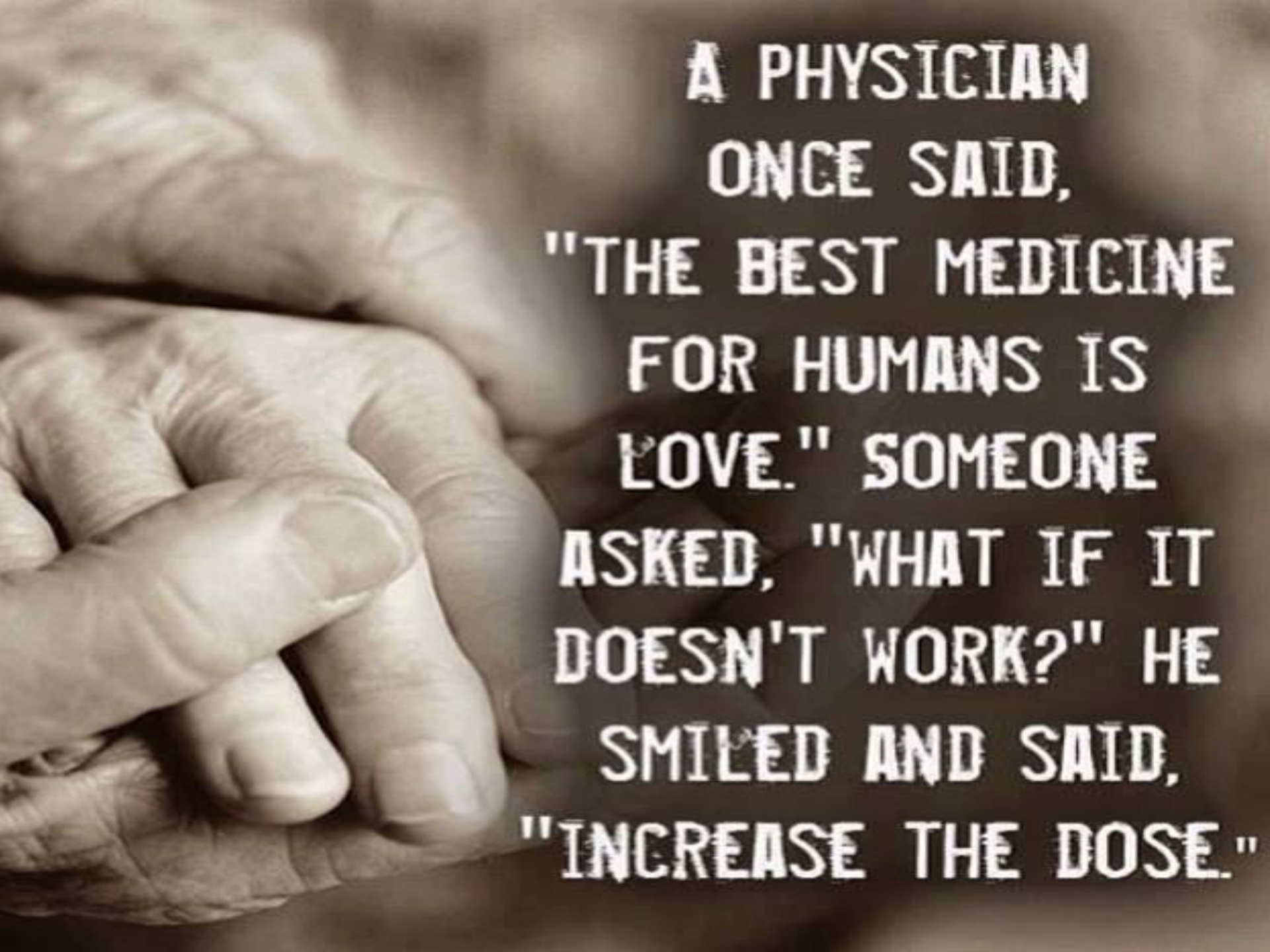
Lactation Risk Categories

ACOG Practice Bulletin 2008

- L 1: SAFEST
- L2: SAFER
- L3: MODERATELY SAFE
- L4: POSSIBLY HAZARDOUS
- L5: CONTRAINDICATED

Psychotropics in Hale's Lactation Categories L1, L4 and L5

Antidepressants	Sertraline L1 – Extensive Data, Compatible Selegiline L4 – No Data, Possibly Hazardous Nefazodone L4 – Limited Data, Possibly Hazardous Doxepin L5 – Limited Data, Hazardous
Mood Stabilizers	Lithium L4 – Significant Data, Possibly Hazardous Valproic Acid L4 – Limited Data, Possibly Hazardous
Antipsychotics	Thioridazine L4 – No Data, Possibly Hazardous
Psychostimulants	Atomoxetine L4 – No Data, Possibly Hazardous Modafinial L4 – No Data, Possibly Hazardous Methamphetamine L5 – Limited Data, Hazardous
Sedatives and Hypnotics	Flunitrazepam L4 – No Data, Possibly Hazardous Flurazepam L4 – No Data, Possibly Hazardous


A PHYSICIAN
ONCE SAID,
"THE BEST MEDICINE
FOR HUMANS IS
LOVE." SOMEONE
ASKED, "WHAT IF IT
DOESN'T WORK?" HE
SMILED AND SAID,
"INCREASE THE DOSE."

Case Study – R.B.

- To ED – harm to self
- Found to be 22 weeks pregnant, malnourished, intellectual disorder . Likely victim of sexual exploitation
- Hallucinations, combative, agitated
- Long inpatient psychiatric stay – difficult community placement
- Decision making capacity determined
- Ethics consultation for management of delivery mode
- Agitated in delivery, medicated
- OVD, bradycardia
- Postpartum care – on medical/psych unit.
- Since discharge – no further contact with health system

Mental Illness and Pregnancy

- Lower fertility rates in women with severe mental illness
  - Bipolar- schizophrenia-borderline personality disorder
- Important to assess for screen for signs/symptoms/history of disorders at all encounters. Recognize that substance abuse is associated with mental illness
- Assess and test for use of prescribed psychiatric medications; educate patient about importance of continued use. Be aware of implications for patient self-stopping all medications because she thinks it is better for the baby.
- Woman is more likely to have increased problems during pregnancy and in first year after birth – can be more severe or arise more quickly
- Patients with previous aggression or violence are more likely to have another incident. Important to explore with patient and providers women's previous history

Nursing Care and Management

- Develop therapeutic relationship with patient
  - Consider primary nursing
  - Non-judgemental
- Motivate patient by encouraging her to do what is best for her baby
- Involve ethics committee early
- Understand decision making capacity in your state. Use caution in taking actions when the patient has the ability to make her own decisions
  - Babbitt, et al. 1/2014 algorithm, American Journal of Obstetrics & Gynecology
- Involve child protection services early

Nursing management-Aggression

- Goal of management in pregnancy is to calm the patient, reduce agitation and risk of aggression, avoid sedation
- Anticipate potential problems, pay attention to gut reactions
- Seek help early to keep yourself and patient safe
  - Have safe environment for patient
  - Do not be alone with patient/blocked by quick exit – protect your safety
- Consider yourself a good monitor of potential crisis
- Know your patient's history
- Be aware of your emotions and how they may influence your actions
- Department wide training for non violent crisis intervention skills

Nursing management - Early signs of Aggression

- Become extremely loud; start shouting
- Become physically tense; appear rigid and tight
- Clench their teeth and hands
- Quite agitated, seemingly anxious and restless; perhaps pacing if mobile; seeming quite jittery
- Have a labile mood, but exhibit mostly anger

Nursing Management - When Violence Erupts

- Be attentive and use early interventions
- Get help from others
- Understand use of emergency medications
- Avoid Mechanical Restraint
  - Significant risk to pregnant patients in advanced pregnancy if placed in supine position for long periods of time
- Staff should stay calm themselves
- Be firm do not negotiate with patient at this level of agitation
- Patients should be shown respect and allowed to maintain their dignity

Pregnancy Outcomes

- Maternal
  - Higher rate of unplanned pregnancy
  - Higher IOL rate- often due to psychiatric condition
  - Higher rate of assisted delivery or emergent C/S
- Neonatal
  - Higher rate of perinatal loss
  - Low birth weight
  - premature

Strategies for care

- Planning conferences for all known patients with communication of plan of care to all disciplines
- Consider introducing patient to environment and assign primary nursing prior to labor or scheduled delivery mode; small group of known staff for patient to interact with
- Introduce patient to equipment, process, experience of L&D, nursery and post partum unit before labor

Strategies for care

- For known patients - Have partnerships with behavioral health clinicians who know and manage the patient
- Identify behavioral health clinicians who can be a resource for staff
- Debrief after event/delivery
- Include these situations in unit simulation and drills
- Develop algorithms; resource binders

Questions

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