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LETTERS

SSRIs AND CONGENITAL DEFECTS

Spontaneous publishing and academic miscarriages (SPAM)

In 1991, in the week that the Food and Drug Administration held regulatory hearings on fluoxetine and suicide, the *BMJ* published an article by Lilly employees exonerating fluoxetine, although the article showed a clear increase in risk with treatment and included under the heading of placebo a suicide that had not happened in the randomised phase of the trials.[1 2] This likely played a part in the way academics worldwide viewed the issues. Since then, in my experience, in the run up to major legal trials or regulatory hearings linked to selective serotonin reuptake inhibitors (SSRIs), one or other major journal has run an article exonerating the drug(s).

In the *BMJ* of 26 September Pedersen and colleagues' article on birth defects and SSRIs points to a risk with treatment.[3] It is accompanied by an editorial minimising these risks by Chambers,[4] who has co-authored other pieces advocating the treatment of antenatal depression with antidepressants. Intriguingly, Chambers has a dataset pointing to a significant 5.1-fold increased odds ratio of major birth defects and a 10.8-fold increased odds ratio of cardiac defects with paroxetine, but these data remain unpublished in the peer reviewed literature almost 10 years after they were first generated.[5]

Last month GlaxoSmithKline opened its defence in the first birth defect case linked to paroxetine to go to trial. What odds that its lead counsel brandished the *BMJ* of 26 September in front of jurors? I have no reason to think that any member of the editorial staff of the *BMJ* has been complicit in any wrongdoing, but there does seem to be something here worthy of further investigation. Chambers argues that the risks of non-treatment outweigh the risks of treatment—despite a doubling of the risk of miscarriage. But do the risks of publishing this editorial outweigh the risks of not publishing it? In other words, is there a need for a filter against spontaneous publishing and academic miscarriages (SPAM)?

CHRISTIAN BAITG/GETTY IMAGES

David Healy professor, Department of Psychiatry, Cardiff University HealyD@cardiff.ac.uk

Competing interests: DH is a witness for the plaintiff in the legal case mentioned in this letter. A complete list of his competing interests is available at www.bmj.com/cgi/eletters/339/sep23_1/b3525#221140

1 Healy D. Did regulators fail over selective serotonin reuptake inhibitors? *BMJ* 2006;333:92-5.
2 Beasley CM, Dornseif BE, Bosomworth JC, Sayler ME, Rampey AH, Heiligenstein JH. Fluoxetine and suicide: a meta-analysis of controlled trials of treatment for depression. *BMJ* 1991;303:685-92.
3 Pedersen LH, Henriksen TB, Vestergaard M, Olsen J, Bech BH. Selective serotonin reuptake inhibitors in pregnancy and congenital malformations: population based cohort study. *BMJ* 2009;339:b3569. (23 September.)
4 Chambers C. Selective serotonin reuptake inhibitors and congenital malformations. The small risk of harm must be balanced against risk of suboptimal or no treatment. *BMJ* 2009;339:b3525. (23 September.)
5 GSK Medicine: paroxetine. Study No: WEUSRTP2280. Available at: www.gsk-clinicalstudyregister.com/files/pdf/24089.pdf

Cite this as: *BMJ* 2009;339:b4293

We selected Christina Chambers from our reviewer database, which listed her specialist interests as perinatal epidemiology and teratology. She has published on SSRIs in pregnancy, including two articles in the *New England Journal of Medicine* that reported adverse outcomes.—Ed

Author's reply

I did not intend my comments to be interpreted as minimising the risk. Rather, I intended to place the risks in context in terms of both size (which is estimated to be comparatively small compared with other known teratogens such as isotretinoin, which can affect more than 20% of exposed pregnancies) and the concomitant risks of no treatment or undertreatment.

Healy mentions our California data on pregnancy outcomes with prenatal exposure to paroxetine. This is a perfect example of the difficulty in drawing conclusions from studies with inadequate sample sizes. Our data on paroxetine were drawn from an ongoing open cohort study with an increasing but still extremely small sample size. Preliminary results were published in abstract form several years ago,[1] and updated results were provided for and included in the meta-analysis recently published by Wurst et al.[2] These same data were also included in a published paper on the cumulative experience with paroxetine and cardiac defects across several teratology information services.[3] Given that our data on the association with cardiac defects had very wide confidence intervals and lacked significance, we deemed that their contribution was most appropriately evaluated in comprehensive meta-analysis.

My comments in this editorial and elsewhere, consistent with the recent joint guidelines from the American Psychiatric Association and American College of Obstetrics and Gynecology, are intended to support the most appropriate treatment of each mother and fetus, recognising that there may be risks from some treatments, as well as from inappropriate treatment, undertreatment, or no treatment.

Christina Chambers associate professor, Division of Dysmorphology and Teratology, Departments of Pediatrics and Family and Preventive Medicine, School of Medicine, University of California San Diego, 9500 Gilman Drive, MC 0828, La Jolla, CA 92093-0828, USA chchambers@ucsd.edu

Competing interests: CC has received grant funding from pharmaceutical companies including Amgen, Abbott, Bristol Myers Squibb, Sanofi-Pasteur, Teva, Sandoz, Kali, Barr, and Apotex, some of which manufacture or distribute selective serotonin reuptake inhibitors (SSRIs).

1 Unfred CL, Chambers CD, Felix R, Kao K, Dick L, Alvarado S, et al. Birth outcomes among pregnant women taking paroxetine (Paxil). Teratology Society 41st annual meeting. June 23-28, 2001, Montreal, Quebec, Canada. Abstracts. *Teratology* 2001;63:211-41.
2 Wurst KE, Poole C, Ephross SA, Olshan AF. First trimester paroxetine use and the prevalence of congenital, specifically cardiac, defects: a meta-analysis of epidemiological studies. *Birth Defects Res Part A Clin Mol Teratol* 2009 Sep 8. [Epub ahead of print]
3 Einarson A, Pistelli A, DeSantis M, Malm H, Paulus WD, Panchaud A, et al. Evaluation of the risk of congenital cardiovascular defects associated with use of paroxetine during pregnancy. *Am J Psychiatry* 2008;165:749-52.

Cite this as: *BMJ* 2009;339:b4295

Women should give informed consent before starting SSRIs

In Pedersen and colleagues' study of selective serotonin reuptake inhibitors (SSRIs) in pregnancy, the hazards were clearest for citalopram and sertraline.[1] However, a meta-analysis of all epidemiologically robust studies of paroxetine in the first trimester of pregnancy conclusively shows increased prevalence of both cardiac malformations (odds ratio 1.46, 95% confidence interval 1.17 to 1.82) and total malformations (1.24, 1.08 to 1.43).[2]

One of the best signals of teratogenicity is an increased rate of spontaneous abortions and a key reason for induced abortion is congenital malformations.[1] Data on SSRIs in 1998 showed that the rate of abortion (spontaneous and induced) was nearly twice as high in those who had taken SSRIs in the first trimester of pregnancy (1.7, 1.1 to 2.9).[3]

Given the limited evidence for effectiveness and these data on potential hazards for the unborn child, the risk-benefit equation is not favourable for SSRIs in pregnancy. The numbers affected are small, but prescribing is widespread in the reproductive years and the consequences are devastating for families. In contrast to the US recommendations,[4] guidelines from the National Institute for Health and Clinical Excellence (NICE) are consistent with the evidence.[5] NICE recommends stopping SSRIs, paroxetine in particular, in pregnancy (or preferably before) and using alternative treatments or tricyclic antidepressants if pharmacotherapy is unavoidable. As the difficulties in stopping SSRI treatment may lead to unavoidable early exposure of the unborn child, women of reproductive age should give informed consent before starting treatment.

Derelie Mangin associate professor and director, Primary Care Research Unit, Department of Public Health and General Practice, University of Otago, Christchurch, New Zealand
dee.mangin@otago.ac.nz

Competing interests: DM is an expert witness for the plaintiff in cases involving Paxil and birth defects. She is also principal investigator in a New Zealand Health Research Council funded randomised controlled trial of SSRI cessation in primary care. She is a member of and was previously on the management committee of Healthy Skepticism. She has been an invited speaker on aspects of rational prescribing at conferences, some of which were sponsored by pharmaceutical companies.

1 Pedersen LH, Henriksen TB, Vestergaard M, Olsen J, Bech BH. Selective serotonin reuptake inhibitors in pregnancy and congenital malformations: population based cohort study. *BMJ* 2009;339:b3569. (23 September.)
2 GSK Medicine: paroxetine. Study No: WEUSRTP2280. Available at: www.gsk-clinicalstudyregister.com/files/pdf/24089.pdf
3 Kulin NA, Pastuszak A, Sage SR, Schick-Boschetto B, Spivey G, Feldkamp M, et al. Pregnancy outcome following maternal use of the new selective serotonin reuptake inhibitors: a prospective controlled multicenter study. *JAMA* 1998;279:609-10.
4 Chambers C. Selective serotonin reuptake inhibitors and congenital malformations. The small risk of harm must be balanced against risk of suboptimal or no treatment. *BMJ* 2009;339:b3525. (23 September.)
5 National Institute for Health and Clinical Excellence. Antenatal and postnatal mental health. Clinical guidelines CG45. 2007. http://guidance.nice.org.uk/CG45

Cite this as: *BMJ* 2009;339:b4292

SSRIs and heart defects in neonates

In a population study, Pedersen and colleagues found a twofold increased risk of septal heart defects after first trimester exposure to selective serotonin reuptake inhibitors (SSRIs).[1] The prevalence increased with citalopram or sertraline but not paroxetine or fluoxetine, and exposure to more than one type of SSRI posed the greatest risk.

We compared the rate of non-syndromic, non-chromosomal congenital heart malformations in newborn infants exposed to SSRIs and unexposed controls.[2] Every newborn infant with a persistent cardiac murmur (even mild) on the second or third day of life was examined by a paediatric cardiologist and had echocardiography. To our knowledge, this screening approach has not been used in previous studies on SSRI exposure.

Echocardiography identified non-syndromic congenital heart defects in 3.4% of exposed babies and in 1.6% of non-exposed controls (relative risk 2.17, 95% confidence interval 1.07 to 4.39). All heart defects were mild: ventricular septal defect, bicuspid aortic valve, and right superior vena cava to coronary sinus. Although our sample was too small to analyse the effects of specific SSRIs, all four (paroxetine, fluoxetine, citalopram, and sertraline) were associated with heart defects.

Our data and clinical experience suggest that women who require treatment with SSRIs during early pregnancy can be reassured that the risk is small and that possible heart malformations are usually mild and often resolve spontaneously. We advise monitoring during early pregnancy, late-targeted ultrasonography, and fetal echocardiography at 22-23 weeks' gestation. Further larger studies using our approach or other methods are still needed.

Gil Klinger deputy director, Neonatal Intensive Care Unit, Schneider Children's Medical Center of Israel, Petah Tiqwa, 49202, Israel
gilkl@post.tau.ac.il
Paul Merlob Beilinson Teratology Information Service (BELTIS), Rabin Medical Center, Petah Tiqwa, 49100, Israel

Competing interests: None declared.

1 Pedersen LH, Henriksen TB, Vestergaard M, Olsen J, Bech BH. Selective serotonin reuptake inhibitors in pregnancy and congenital malformations: population based cohort study. *BMJ* 2009;339:b3569. (23 September.)
2 Merlob P, Birk E, Sirota L, Linder N, Berant M, Stahl B, et al. Are selective serotonin reuptake inhibitors cardiac teratogens? Echocardiographic screening of newborns with persistent heart murmur. *Birth Defects Res Part A* 2009 Aug 18. [Epub ahead of print]

Cite this as: *BMJ* 2009;339:b4288

Case registers in pregnancy?

Did Pedersen and colleagues[1] find any clinically significant effects of selective seretonin reuptake inhibitors on birth weight, spontaneous abortion, or persistent pulmonary hypertension of the newborn?

Instead of retrospective cohort studies, might case registers for pregnancy and depression similar to prospective epilepsy and pregnancy registers[2] be set up in developed countries with robust monitoring systems by general practitioners and obstetricians? Such registers have achieved prominence with the advent of electronic case records and the technological capacity to derive anonymous databases from them.[3]

Devender Singh Yadav staff grade psychiatrist, Princess of Wales Hospital, Bridgend CF31 1RQ **dsyadav@doctors.org.uk**

Competing interests: None declared.

1 Pedersen LH, Henriksen TB, Vestergaard M, Olsen J, Bech BH. Selective serotonin reuptake inhibitors in pregnancy and congenital malformations: population based cohort study. *BMJ* 2009;339:b3569. (23 September.)
2 Morrow J, Russell A, Guthrie E, Parsons L, Robertson I, Waddell R, et al. Malformation risks of anti-epileptic drugs in pregnancy: a prospective study from the UK Epilepsy and Pregnancy Register. *J Neurol Neurosurg Psychiatry* 2006;77:193-8.
3 Perera G, Soremekun M, Breen G, Stewart R. Case register: noble past, challenging present, exciting future. *Br J Psychiatry* 2009;195:191-3.

Cite this as: *BMJ* 2009;339:b4286

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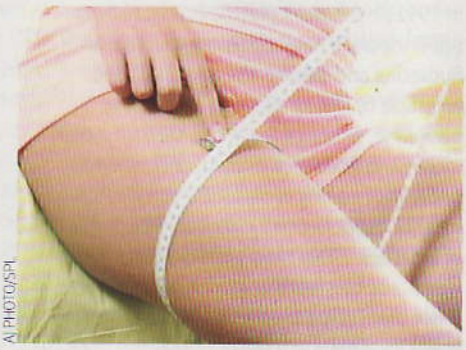

A PHOTO/SPL

THIGHS AND HEART DISEASE

Thighs and thresholds

According to the abstract of Heitmann and Frederiksen's paper, "a threshold effect for thigh circumference was evident, with greatly increased risk of premature death below around 60 cm."[1] Table 1 shows that the median thigh circumference was around 55 cm, implying that more than half the population were at greatly increased risk. In contrast to the misleading abstract and press release,[2] the BMJ Group provided a more appropriate interpretation in the *Guardian*: "Having thighs larger than 60 cm made no difference to people's risk. People were most at risk if they had a thigh measurement of less than 46.5 cm (18 inches). This group had roughly double the chances of getting heart and circulation problems or dying during the study. However, only 2.5% of the people fell into this category."[3]

Particularly in men, the reported effects were modest before analyses were adjusted for anthropometric measures such as body mass index and waist circumference. These adjusted estimates are hard to interpret because they refer to the differences in risk that would apply if a person changed his or her thigh circumference while keeping the other anthropometric measures constant.

The accompanying editorial also seemed to ignore these issues in interpretation.[4]

Roger M Harbord medical statistician
roger.harbord@bristol.ac.uk
Jonathan A C Sterne professor of medical statistics and epidemiology, Department of Social Medicine, University of Bristol, Canynge Hall, Bristol BS8 2PS