

# Should we stop using tricyclic antidepressants in pregnancy?

C. M. Pariante<sup>1,2\*</sup>, G. Seneviratne<sup>1</sup> and L. Howard<sup>2,3</sup>

<sup>1</sup> Section of Perinatal Psychiatry and Stress, Psychiatry and Immunology, Department of Psychological Medicine, Institute of Psychiatry, King's College London, London, UK

<sup>2</sup> National Institute for Health Research 'Biomedical Research Centre for Mental Health', Institute of Psychiatry and South London and Maudsley NHS Foundation Trust, London, UK

<sup>3</sup> Section of Women's Mental Health, Health Service and Population Research Department, Institute of Psychiatry, King's College London, London, UK

A new Swedish study by Reis & Källén describes approximately 15 000 women (and their babies) that, between 1995 and 2007, reported the use of antidepressants, or were prescribed such drugs, during pregnancy. In this study, pregnancy and teratogenic outcomes after exposure to tricyclic antidepressants are, for most measures, equal or worse than after exposure to selective serotonin reuptake inhibitors or other antidepressants. Based on this and on a review of the few other studies available (admittedly, a relatively small number of women on which conclusions can be based), the authors of this Editorial challenge the 'perinatal myth' that tricyclics are the safest choice in pregnancy.

Received 24 November 2009; Revised 23 January 2010; Accepted 25 January 2010; First published online 10 March 2010

**Key words:** Antidepressants, depression, pregnancy, selective serotonin reuptake inhibitors, tricyclics.

A recent *British Medical Journal* paper (Pedersen *et al.* 2009) and the accompanying editorial (Chambers, 2009) on the teratogenic effects of selective serotonin reuptake inhibitors (SSRIs) have yet again brought attention to the risks and benefits of prescribing antidepressants in pregnancy, and have attracted public attention (BBC News Online, 2009). Now a new Swedish study by Reis & Källén (2010) is the most recent addition to the growing evidence in this area. This study confirms that a significant proportion of women are depressed in pregnancy. We know that this can lead to adverse outcomes for both the mother and the baby [National Institute for Health and Clinical Excellence (NICE), 2007], particularly for women with severe depression who will not be effectively treated with psychological therapy alone, and therefore will need antidepressant treatment in pregnancy. However, when studying the potential risks of antidepressants, it is very difficult to separate the effects of the drugs from the effects of depression (and its biological abnormalities) or from the behavioural consequences of depression: smoking, obesity, alcohol and (lack of) folic acid intake. Reassuringly, this study and

other recent studies find that, if there is an increased risk for congenital malformations and other adverse effects by antidepressants, the absolute risk for the individual pregnant woman is very low. These messages are consistent across the 2007 UK NICE Guidelines for Antenatal and Postnatal Mental Health (National Institute for Health and Clinical Excellence, 2007), the 2008 British Association of Psychopharmacology Guidelines for Depression (Anderson *et al.* 2008), the recent joint report from the American Psychiatric Association (APA) and the American College of Obstetricians and Gynecologists (ACOG) (Yonkers *et al.* 2009), and the 2009 Maudsley Prescribing Guidelines (Taylor *et al.* 2009). So what does this new Swedish study by Reis & Källén (2010) add to the literature?

Let's step back a little. Common wisdom maintains that tricyclic antidepressants, because they have been around for much longer than novel SSRIs or other antidepressants, are the safest choice in pregnancy. Of course, it is true that during their many decades of use, no major teratogenic effects have been observed with tricyclics. In contrast, SSRIs have been used for a much shorter period of time, and so less might be known about their effects. However, official guidelines stating that tricyclics have lower known risks should base their conclusion on evidence. But is the evidence really there, or is it just a perinatal myth?

The joint APA and ACOG report concludes that 'the majority of studies have not shown an association

---

\* Address for correspondence: Dr C. M. Pariante, Section of Perinatal Psychiatry and Stress, Psychiatry and Immunology, Room 2-055, The James Black Centre, 125 Coldharbour Lane, London SE5 9NU, UK.  
(Email: carmine.pariante@kcl.ac.uk)

between TCA use in pregnancy and structural malformations' (Yonkers *et al.* 2009). However, they cite only two papers: Altshuler *et al.* (1996) and Simon *et al.* (2002). The first paper is a meta-analysis of studies published between 1966 and 1995. The authors also conclude that tricyclic antidepressants do not seem to confer increased risk for 'organ dysgenesis', but this is based on 414 patients exposed during the first trimester, collected across 13 small studies. The second study examines a total of 209 infants exposed to tricyclics (and 185 to SSRIs) and finds no evidence of congenital malformations for either class of drugs. So, no superiority for tricyclics here. The recently published *Maudsley Prescribing Guidelines* (Taylor *et al.* 2009), in its section on 'Drug choice in pregnancy' (to which the authors of this editorial have contributed), again conclude that tricyclics 'have been widely used throughout pregnancy without apparent detriment to the foetus and have for many years been agents of choice in pregnancy'. They also cite two studies: Kallen (2004) and Davis *et al.* (2007). The paper by Kallen (2004) includes data which are used in Reis & Källén's larger dataset, and therefore we will discuss the overall findings below. The study by Davis *et al.* (2007), comparing 805 mothers exposed to SSRIs and 167 exposed to tricyclics, concludes that SSRIs and tricyclics do not show a 'consistent link with congenital anomalies' (so, again, no superiority of tricyclics). It is of interest that, of the studies mentioned so far, two also examine other pregnancy outcomes: Davis *et al.* (2007) find that both SSRIs and tricyclics exposures during the third trimester are associated with an increased risk for respiratory distress syndrome, endocrine and metabolic disturbances, with no differences between classes; and Simon *et al.* (2002) find evidence that tricyclics are better than SSRIs, as only SSRIs during pregnancy are associated with earlier delivery and consequent lower birth weight and lower Apgar scores.

So, what does this new Swedish study by Reis & Källén (2010) add, and should we indeed stop tricyclic use in pregnancy? This study describes approximately 15 000 women (and their babies) that, between 1995 and 2007, reported the use of antidepressants, or were prescribed such drugs, during pregnancy. These women were compared with all other women who gave birth in the same period: approximately 1 million women and 1.2 million babies. Most women took SSRIs ( $n=10\,170$ ) but a reasonable number (and the largest published so far) took tricyclics (1662 women, which for 1208 was clomipramine); 1351 took other antidepressants, mostly venlafaxine ( $n=859$ ). This paper has three very interesting findings. First, there is an association between antidepressant treatment and pre-existing diabetes and chronic hypertension. This

indicates that, in addition to the biological and behavioural consequences mentioned above (or, perhaps, because of those), depression in pregnancy is itself associated with higher medical morbidity – an additional confounder in this already complex set of questions. Second, the increased risk of persistent pulmonary hypertension of the newborn after SSRIs has been confirmed. Considering that this is a rare event and the previous literature has been inconclusive, this is a definitive and irrefutable step forward. It is important to emphasize, however, that the absolute risk of persistent pulmonary hypertension after SSRIs remains low, with an odds ratio of 3.4 (the baseline rate in the Swedish population is 0.56 per 1000). Finally, and most relevant to this editorial, outcomes after exposure to tricyclics are, for most measures, equal or worse than after exposure to SSRIs or other antidepressants. For example, there is a tendency for a higher risk of preterm birth and low birth weight after tricyclics than after SSRIs. Moreover, the risks for hypoglycaemia, respiratory diagnoses and low Apgar score are significantly increased primarily after the use of tricyclics, but also of SSRIs; and an increased risk for jaundice is present after exposure to tricyclics and other antidepressants, but not SSRIs. Even more important, the risks for a relatively severe malformation, for any cardiovascular defects, for ventricular septum defects, or for atrial septum defects, are all significantly increased only for tricyclics and for one SSRI, paroxetine. Paroxetine is already considered contraindicated in pregnancy (National Institute for Health and Clinical Excellence, 2007; Taylor *et al.* 2009).

In their paper, Reis & Källén (2010) discuss the main limitations of their study – most notably, that the findings could be confounded by 'indication', that is, that women prescribed tricyclics could be clinically different from those prescribed SSRIs. Moreover, most women receiving tricyclics were, in fact, receiving clomipramine, a tricyclic with a strong serotonergic component and, anecdotally, not widely used in the UK. Finally, even if this is the largest published sample of mothers prescribed tricyclics, this study is based on a relatively small number of women, and therefore we still have only limited data on which we can base our conclusions. However, the notion of a 'superiority' of tricyclics has been challenged, and this cannot be ignored in clinical practice. Other authors have clearly argued that SSRIs, when used in the general population, are much safer drugs, especially in overdoses, than tricyclics, and that continuing to prescribe tricyclic antidepressants in the general population has scandalous consequences, including an excess of 3500 deaths by overdose in the decade up to 2004 (Nutt, 2005). The NICE Antenatal and Postnatal

Mental Health Guidelines (National Institute for Health and Clinical Excellence, 2007) also clearly state that 'most tricyclic antidepressants have a higher fatal toxicity index than SSRIs'. In view of the lack of any evidence indicating superiority of tricyclics for pregnancy or teratogenic outcomes, we believe that this class of drugs can no longer be considered the safest choice in pregnancy.

### Acknowledgements

None.

### Declaration of Interest

In the last 5 years, C.M.P has received speakers' fees and travel honoraria from the following pharmaceutical companies: Eli Lilly, Innova Pharma Recordati, Janssen, Organon, Takeda, and Wyeth.

### References

- Altshuler LL, Cohen L, Szuba MP, Burt VK, Gitlin M, Mintz J** (1996). Pharmacologic management of psychiatric illness during pregnancy: dilemmas and guidelines. *American Journal of Psychiatry* **153**, 592–606.
- Anderson IM, Ferrier IN, Baldwin RC, Cowen PJ, Howard L, Lewis G, Matthews K, Lister-Williams RH, Peveler RC, Scott J, Tylee A** (2008). Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 2000 British Association for Psychopharmacology guidelines. *Journal of Psychopharmacology* **22**, 343–396.
- BBC News Online** (2009). (<http://news.bbc.co.uk/1/hi/health/8273350.stm>).
- Chambers C** (2009). Selective serotonin reuptake inhibitors and congenital malformations. *British Medical Journal* **339**, b3525.
- Davis RL, Rubanowice D, McPhillips H, Raebel MA, Andrade SE, Smith D, Yood MU, Platt R** (2007). Risks of congenital malformations and perinatal events among infants exposed to antidepressant medications during pregnancy. *Pharmacoepidemiology and Drug Safety* **16**, 1086–1094.
- Kallen B** (2004). Neonate characteristics after maternal use of antidepressants in late pregnancy. *Archives of Pediatrics and Adolescent Medicine* **158**, 312–316.
- National Institute for Health and Clinical Excellence** (2007). *Antenatal and Postnatal Mental Health*. Alden Press: Leicester, UK.
- Nutt DJ** (2005). Death by tricyclic: the real antidepressant scandal? *Journal of Psychopharmacology* **19**, 123–124.
- Pedersen LH, Henriksen TB, Vestergaard M, Olsen J, Bech BH** (2009). Selective serotonin reuptake inhibitors in pregnancy and congenital malformations: population based cohort study. *British Medical Journal* **339**, b3569.
- Reis M, Källén B** (2010). Delivery outcome after maternal use of antidepressant drugs in pregnancy: an update using Swedish data. *Psychological Medicine*. Published online: 5 January 2010. doi:10.1017/S0033291709992194.
- Simon GE, Cunningham ML, Davis RL** (2002). Outcomes of prenatal antidepressant exposure. *American Journal of Psychiatry* **159**, 2055–2061.
- Taylor D, Paton C, Kapur S** (2009). *The Maudsley Prescribing Guidelines*, 10th edn. Informa Healthcare: London.
- Yonkers KA, Wisner KL, Stewart DE, Oberlander TF, Dell DL, Stotland N, Ramin S, Chaudron L, Lockwood C** (2009). The management of depression during pregnancy: a report from the American Psychiatric Association and the American College of Obstetricians and Gynecologists. *General Hospital Psychiatry* **31**, 403–413.