



HAL
open science

Comment on: "Should Antidepressants be Avoided in Pregnancy?"

Alain Braillon, Susan Bewley, Aubrey Blumsohn, Florian Naudet

► **To cite this version:**

Alain Braillon, Susan Bewley, Aubrey Blumsohn, Florian Naudet. Comment on: "Should Antidepressants be Avoided in Pregnancy?". *Drug Safety*, 2023, 46 (6), pp.615-616. 10.1007/s40264-023-01308-1 . hal-04088824

HAL Id: hal-04088824

<https://hal.science/hal-04088824>

Submitted on 13 Jul 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

1
2
3
4 Comment on: Should Antidepressants be Avoided in Pregnancy?

5
6
7 Alain Brailion (1), Susan Bewley (2), Aubrey Blumsohn (3), Florian Naudet (4)

8
9
10 (1) 80000 Amiens, France, corresponding author at brailion.alain@gmail.com

11
12 (2) Obstetrics and Women's Health, King's College London, London, UK.

13
14 (3) Sheffield, UK.

15
16 (4) Therapeutics, Adult Psychiatry Department and Clinical Investigation Center (INSERM 1414),
17 University Hospital, Rennes, France.

18
19
20
21 Declarations

22
23
24 Funding: Not applicable.

25
26
27 Conflict of interest: Alain Brailion, Susan Bewley and Florian Naudet are among in industry-independent
28 experts from Jeanne Lenzer's list.(<https://jeannelenzer.com/list-independent-experts>) SBs declaration of
29 interests can be found at [whopaysthisdoctor](http://whopaysthisdoctor.com).

30
31
32
33
34 Ethics approval: Not applicable.

35
36
37 Consent to participate: Not applicable.

38
39
40
41 Consent for publication: Not Applicable

42
43
44 Availability of data and material: Data sharing is not applicable to this article as no datasets were
45 generated or analysed during the current study.

46
47
48
49 Code availability (software application or custom code): Not applicable.

50
51
52
53 Authors' contribution: Alain Brailion, Susan Bewley, Aubrey Blumsohn, Florian Naudet have been
54 exchanging about this topic. Alain Brailion wrote a first draft. All authors have reviewed and approved the
55 final version.

56
57
58
59 556w. and 18 ref. (limit: 1000 w., do not include references)

60
61
62
63
64
65

1
2
3
4
5
6 Dear Editor,

7 We commend Besag and Vasey for reviewing adverse outcomes in offspring (preterm birth, birth defects,
8 neurodevelopmental disorders) associated with antidepressant exposure during pregnancy. Although they
9 used published studies comparing exposed and unexposed siblings to limit some types of bias such as
10 reverse causation and residual confounding [1], important questions remain.
11
12
13
14

15
16 Firstly, we do not agree with authors' claim that the "few statistically significant differences in single
17 studies were small and possibly not clinically significant" [1] challenges. From a public health
18 perspective, even "small" risks can have large and devastating consequences when antidepressant
19 prescription is so frequent; up to 5.5% during pregnancy in North America [2]. "Not clinically significant"
20 is a personal conclusion that has no place in patient-centred care as harm pertains to the recipient, not the
21 prescriber. Only properly informed women should make the value judgment using graspable information.
22 Kolding and colleagues, using a Danish registry, provided a clear Number Needed to Harm when
23 analyzing the risk of cardiac malformations with antidepressant use during the first trimester of pregnancy,
24 e.g., for venlafaxine: 307 for severe cardiac malformations, 225 for hypoplastic left heart syndromes, 90
25 for remaining cardiac malformations.[3] Certainly, evidence for harm can be controversial as
26 observational studies are prone to biases. However, some complications that align with pathophysiology
27 were not studied by Besag and Vasey. For example, preeclampsia and postpartum hemorrhage are
28 reported as raised - in line with other effects of antidepressants on the cardiovascular system, platelet-
29 mediated hemostasis and myometrial contractility [4] - as are neonatal respiratory distress with intensive
30 care unit admission and persistent pulmonary hypertension [5,6]. Additionally, debates about
31 teratogenicity and neurodevelopmental toxicities cannot ignore 'red-flags' from experimental studies [7-
32 10]. Prescribers should assume that antidepressants are causative unless robustly proven otherwise.
33
34
35
36
37
38
39
40
41
42
43
44

45
46 Secondly, Besag and Vasey should have discussed the serious limitations of their review. The power of
47 the studies that were included is low: a) antidepressants are analyzed as a homogenous class while adverse
48 effects are product-specific, e.g. escitalopram/citalopram have the most serious adverse cardio-vascular
49 effects; b) the series are small. Further, the findings of the largest series show that antidepressants in
50 pregnancy are associated with diminished performance in mathematics standardized tests among Danish
51 schoolchildren [11]. This is dismissed by Besag and Vasey, whereas the specificities of the Danish School
52 system and a dose response of effects make the finding more worrying [12].
53
54
55
56
57
58
59
60
61
62
63
64
65

1
2
3
4 Thirdly, the authors rightly concluded that “decisions on antidepressant treatment during pregnancy
5 should be made individually based on evidence from properly controlled studies” [1]. However, they fail
6 to acknowledge that there is no evidence that antidepressants are superior to psychotherapy on clinically
7 relevant outcomes in the general population [13-17]. Indeed, antidepressants vs placebo trials are only
8 short-term (6-8 weeks) and the clinical relevance of the depression rating scales is questionable (highly
9 clinically relevant well-being/functional outcomes form only 1 out of 17 items of the Hamilton Depression
10 Rating Scale and they are entirely absent from the Montgomery-Åsberg Depression Rating Scale). Lastly,
11 there are no controlled studies showing that antidepressants could improve obstetric or mental health
12 outcomes or have clinically meaningful effects on maternal-infant attachment. Pregnancy is a specific
13 condition deserving specific investigation.
14
15
16
17
18
19
20
21

22 Besag has previously written about the language used to declare or infer that drugs are “safe”, and the
23 evidence required to use that term [18]. We are unconvinced this latest publication fits well within that
24 laudable framework.
25
26
27
28
29
30

31 References

- 32 1. Besag FMC, Vasey MJ. Should Antidepressants be Avoided in Pregnancy?. *Drug Saf.* 2023;46:1-17.
- 33 2. Anderson KN, Lind JN, Simeone RM et al. Maternal Use of Specific Antidepressant Medications
34 During Early Pregnancy and the Risk of Selected Birth Defects. *JAMA Psychiatry.* 2020;77:1246–55.
- 35 3. Kolding L, Ehrenstein V, Pedersen L, et al. Antidepressant use in pregnancy and severe cardiac
36 malformations: Danish register-based study. *BJOG.* 2021;128:1949-1957.
- 37 4. Palmsten K, Chambers CD, Wells A, Bandoli G. Patterns of prenatal antidepressant exposure and risk
38 of preeclampsia and postpartum haemorrhage. *Paediatr Perinat Epidemiol.* 2020;34:597-606.
- 39 5. Bandoli G, Chambers CD, Wells A, Palmsten K. Prenatal Antidepressant Use and Risk of Adverse
40 Neonatal Outcomes. *Pediatrics.* 2020;146:e20192493.
- 41 6. Hoyer D. Targeting the 5-HT system: Potential side effects. *Neuropharmacology.* 2020;179:108233.
- 42 7. Cabrera RM, Linda Lin Y, Law E, Kim J, Wlodarczyk BJ. The teratogenic effects of sertraline in
43 mice. *Birth Defects Res.* 2020;112:1014-1024.
- 44 8. Warkus ELL, Marikawa Y. Fluoxetine Inhibits Canonical Wnt Signaling to Impair Embryoid Body
45 Morphogenesis: Potential Teratogenic Mechanisms of a Commonly Used Antidepressant. *Toxicol Sci.*
46 2018;165:372-388.
- 47 9. Liao CC, Lee LJ. Neonatal fluoxetine exposure affects the action potential properties and dendritic
48 development in cortical subplate neurons of rats. *Toxicol Lett.* 2011;207:314-321.
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

- 1
2
3
4 10. Lugo-Candelas C, Cha J, Hong S, et al. Associations Between Brain Structure and Connectivity in
5
6 Infants and Exposure to Selective Serotonin Reuptake Inhibitors During Pregnancy. *JAMA Pediatr.*
7
8 2018;172:525-33.
- 9 11. Christensen J, Trabjerg BB, Sun Y, Dreier JW. Association of Maternal Antidepressant Prescription
10
11 During Pregnancy With Standardized Test Scores of Danish School-aged Children. *JAMA.*
12
13 2021;326:1725-1735.
- 14 12. Braillon A. Association of Maternal Antidepressant Prescription During Pregnancy and Danish
15
16 School-aged Children's Standardized Test Scores. *JAMA.* 2022;327:781-782.
- 17 13. Amick HR, Gartlehner G, Gaynes BN, et al. Comparative benefits and harms of second generation
18
19 antidepressants and cognitive behavioral therapies in initial treatment of major depressive disorder:
20
21 systematic review and meta-analysis. *BMJ.* 2015;351:h6019.
- 22 14. Munkholm K, Paludan-Müller AS, Boesen K. Considering the methodological limitations in the
23
24 evidence base of antidepressants for depression: a reanalysis of a network meta-analysis. *BMJ Open.*
25
26 2019;9:e024886.
- 27 15. Leichsenring F, Steinert C, Rabung S, Ioannidis JPA. The efficacy of psychotherapies and
28
29 pharmacotherapies for mental disorders in adults: an umbrella review and meta-analytic evaluation of
30
31 recent meta-analyses. *World Psychiatry* 2022;21:133-145. doi: 10.1002/wps.2094.
- 32 16. Kolovos S, Kleiboer A, Cuijpers P. Effect of psychotherapy for depression on quality of life: meta-
33
34 analysis. *Br J Psychiatry.* 2016;209:460-8
- 35 17. Stone MB, Yaseen ZS, Miller BJ, Richardville K, Kalaria SN, Kirsch I. Response to acute
36
37 monotherapy for major depressive disorder in randomized, placebo controlled trials submitted
38
39 to the US Food and Drug Administration: individual participant data analysis. *BMJ.*
40
41 2022;378:e067606.
- 42 18. Besag FM, Dodd S. When can a drug be declared "safe"? *Curr Drug Saf.* 2010;5:112-3.
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65