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Selective Serotonin Reuptake Inhibitor (SSRI) Antidepressants in Pregnancy and Congenital Anomalies: Analysis of Linked Databases in Wales, Norway and Funen, Denmark

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Abstract

Background

Hypothesised associations between in utero exposure to selective serotonin reuptake inhibitors (SSRIs) and congenital anomalies, particularly congenital heart defects (CHD), remain controversial. We investigated the putative teratogenicity of SSRI prescription in the 91 days either side of first day of last menstrual period (LMP).

Methods and Findings

Three population-based EUROCAT congenital anomaly registries—Norway (2004–2010), Wales (2000–2010) and Funen, Denmark (2000–2010)—were linked to the electronic healthcare databases holding prospectively collected prescription information for all pregnancies in the timeframes available. We included 519,117 deliveries, including foetuses terminated for congenital anomalies, with data covering pregnancy and the preceding quarter, including 462,641 with data covering pregnancy and one year either side. For SSRI exposures 91 days either side of LMP, separately and together, odds ratios with 95% confidence intervals (ORs, 95%CI) for all major anomalies were estimated. We also explored: pausing or discontinuing SSRIs preconception, confounding, high dose regimens, and, in Wales, diagnosis of depression. Results were combined in meta-analyses. SSRI prescription 91 days either side of LMP was associated with increased prevalence of severe congenital heart defects (CHD) (as defined by EUROCAT guide 1.3, 2005) (34/12,962 [0.26%] vs. 865/506,155 [0.17%], OR 1.50, 1.06–2.11), and the composite adverse outcome of 'anomaly or stillbirth' (473/12,962, 3.65% vs. 15829/506,155, 3.13%, OR 1.13, 1.03–1.24). The
increased prevalence of all major anomalies combined did not reach statistical significance (3.09% [400/12,962] vs. 2.67% [13,536/506,155] OR 1.09, 0.99–1.21). Adjusting for socio-economic status left ORs largely unchanged. The prevalence of anomalies and severe CHD was reduced when SSRI prescriptions were stopped or paused preconception, and increased when >1 prescription was recorded, but differences were not statistically significant. The dose-response relationship between severe CHD and SSRI dose (meta-regression OR 1.49, 1.12–1.97) was consistent with SSRI-exposure related risk. Analyses in Wales suggested no associations between anomalies and diagnosed depression.

Conclusion
The additional absolute risk of teratogenesis associated with SSRIs, if causal, is small. However, the high prevalence of SSRI use augments its public health importance, justifying modifications to preconception care.

Introduction
Exposure to selective serotonin reuptake inhibitors (SSRIs) during the first trimester of pregnancy, including the crucial period of organogenesis (the first 49 days after implantation)[1], affects 4% of pregnant women in the USA[2] and UK[3]. SSRI prescribing indications, mainly depression, panic, obsessive-compulsive or social anxiety disorders, and, for fluoxetine, bulimia nervosa, are not always recorded [3]. SSRIs, particularly fluoxetine and citalopram, and their metabolites, cross the placenta[4], and appear in cord blood[5,6]; their presence in amniotic fluid prolongs foetal exposure. SSRIs, and some other antidepressants, act on the crucial serotonin transporter (SERT, aka 5HTT, SLC6A4, OMIM 182138), which regulates the synaptic concentration of serotonin (5HT) in many tissues, including the placenta[7]. The resultant increased bioavailability of serotonin affects vasoconstriction and coagulation or bruising [6,8,9], cardiac morphogenesis [10,11], CNS development[6] gastrulation, laterality and craniofacial development[10], conferring biological plausibility on reported associations between SSRI exposure during organogenesis and certain congenital anomalies.

The full impact of exposure to SSRIs in utero is incompletely understood, and not all problems initially suspected [12] have been confirmed by further investigation. Some[13–22], but not all[17–22], observational studies indicate significant associations between SSRI exposure during organogenesis and all congenital anomalies combined. Risks may be confined to specific SSRIs and specific anomalies[23,24]. However, the literature offers no consistency: paroxetine is implicated in some studies[24],[25], and fluoxetine[24,26,27], citalopram/ escitalopram [17,27] and sertraline[17,28] in others. Meta-analyses[26,29,30] and analysis of 12 EUROCAT registries[31] indicate an overall association between SSRI exposure and congenital heart defects (CHD); however, there is no consensus[21,22,29,32,33]. The most persistent associations relate to paroxetine exposure and CHD[22,24,27,30,31], particularly at doses >25mg/day [34]. Epidemiologists also report increased risks of: neural tube defects[33,35], ano-rectal stenosis/ atresia[23], gastrochisis, omphalocele[35], renal dysplasia, hypospadias[27], limb reduction[23], talipes equinovarus (clubfoot)[23], craniosynostosis[35], anomalies of the eye [18], ear, face[36], respiratory[36] and digestive tracts[15,24].

To investigate the putative teratogenicity of SSRIs, three countries from the pan-European congenital anomalies registry network[37,38] were linked with healthcare databases. We
aimed to examine any associations between major congenital anomalies and: prescription of antidepressant medicines in the 91 days either side of the 1st day of last menstrual period (LMP); high dose SSRI regimens; confounding; pausing or stopping SSRI pharmacotherapy before pregnancy; and diagnosed, unmedicated depression.

Methods
Three population-based cohorts containing prospectively collected linked prescription data were interrogated using a common protocol. Ethical and data access approvals were obtained for each country from the relevant governance infrastructures (see acknowledgements).

Settings
Three congenital anomalies registries that contribute to EUROCAT[37,39] were linked with prescription and healthcare databases covering their source populations[40,41]. We examined anonymised linked routinely collected data on congenital anomalies, primary care prescribing (Wales) or dispensing (Denmark, Norway), concurrent maternal diagnoses and demographic indicators from:

1. Denmark’s Medical Birth registry, Danish national Prescription and Patient registers, Statistics Denmark[42] and the Funen, Denmark (Odense) EUROCAT register.
2. Norway’s Medical Birth Registry, containing all EUROCAT cases, linked to the National Prescription Database and the National Education Database[43,44].
3. Wales’ health and social care linked electronic databank (the Secure Anonymised Information Linkage [SAIL]). SAIL links primary care records, including prescriptions, for ~40% of the population to the Office of National Statistics births and deaths register, the National Community Child Health Database (NCCHD), the Patient Episode Database for Wales and CARIS (Congenital Anomaly Register and Information Service for Wales). All general practices were invited to participate, without payment, and ~40% had done so in 2014[45,46].

Databases were linked by trusted third parties (Statistics Denmark, Statistics Norway in conjunction with the National Prescription Database, NHS Wales Informatics Service) using unique personal identifiers, which remained undisclosed to researchers, ensuring anonymity.

The 3 countries have similar population sizes and life expectancies, but differ in: GDP per capita (Wales $23.90k[47] Denmark $50.46, Norway $72.96K[48]); the proportion of children living in poverty, defined as <60% median household income (Wales 28%[49], Denmark 7% and Norway 8%[50]); and unemployment rates (Wales 5.3%, Denmark 3.9% and Norway 3.4%)[47,48], (2006 data). Much of Wales is an EU Convergence area [51].

Study population
The study population included all foetuses and infants who 1) would have appeared in the EUROCAT registries had they been diagnosed with a major congenital anomaly, 2) had linked maternal prescription data, and 3) whose birth outcome was either live birth or still birth/ late foetal death after 20 weeks (24 weeks in Wales) or termination of pregnancy for foetal anomaly (TOPFA) recorded in the EUROCAT register. Deliveries from 1st January 2000 to 31st December 2010 were included in Wales and Denmark. In Norway, all pregnancies with date of LMP after April 1st 2004 and ending before 31st December 2010 were included, to coincide with the start of the prescription database. In Wales, infants were included where the associated maternal ID was in the geographical areas that could be linked with the primary care dataset and the
We prepared 2 datasets with an inclusion criterion relating to the woman’s time on the linked database with prescription information:

1. 91 days before LMP to delivery (birth or TOPFA) (main analysis)
2. 365 days before LMP to 365 days after delivery

Information on start of pregnancy was obtained from ultrasound scan data recorded in the Medical Birth Registers of Norway and Denmark (MBRN, MBRD), and the NCCHD for Wales [41]. Representivity was checked in Denmark and Wales by comparing socioeconomic status (SES) with national populations.

**Exposure**

Exposure was defined as one or more prescription for an antidepressant issued (Wales) or dispensed (Norway & Denmark) 91 days either side of the first day of LMP. We based our timeframe on prescription duration (typically 90 days) and relevant pharmacokinetic parameters: for example elimination of the active metabolite of fluoxetine can take ~40 days in adults[52], and longer in the embryo or foetus[11]. Antidepressants were investigated according to anatomical, therapeutic, chemical (ATC) classification [53]: 1) grouped a) all SSRIs (NO6AB); b) all antidepressants (NO6A); 2) as individual SSRIs, fluoxetine, citalopram, paroxetine, sertraline, escitalopram, fluvoxamine. Where more than one SSRI had been prescribed, exposure was not allocated to either SSRI; women switching were retained as SSRI exposed. Where non-SSRI antidepressants were co-prescribed, exposure was classified according to the SSRI. Denmark supplied data on SSRIs only.

**Dose**

was calculated from tablet and capsule sizes, to avoid missing data. We classified high dose exposure as prescription of: 60mg fluoxetine, 40mg citalopram, 30mg paroxetine, 100mg sertraline, 20mg escitalopram, based on tablet/ capsule sizes quoted in the British National Formulary (BNF)[54]. Smaller tablets and capsules were classified as ‘other dose’ (low or medium).

**Outcomes**

Major congenital anomalies were classified according to the EUROCAT standard subgroups, as defined in EUROCAT Guide 1.3, chapter 2.2 [37]. Severe CHD was defined as ICD10 codes: Q200 (common arterial trunk), Q203 (discordant ventriculoarterial connection), Q204 (double inlet ventricle), Q212 (atrioventricular septal defect), Q213 (tetralogy of Fallot), Q220 (pulmonary valve atresia), Q224 (tricuspid stenosis or atresia), Q225 (Ebstein’s anomaly), Q226 (hypoplastic right heart), Q230 (stenosis or atresia of aortic valve), Q234 (hypoplastic left heart), Q251 (co-arcation of aorta), Q262 (total anomalous pulmonary venous connection). Patent ductus arteriosus in pre-term infants was not included as CHD. Minor anomalies are not recorded in EUROCAT, and not investigated. Congenital anomaly cases, diagnosed within the first year of life, irrespective of mother’s time on database, were as reported to EUROCAT: October 2014 (Wales), February 2012 (Denmark), February 2014 (Norway). We excluded, from the main analysis, subjects with anomalies of chromosomal (EUROCAT subgroup al88) or genetic (al104, al105 & al108) aetiology, including sequences[37].

We analysed as prior hypotheses associations between SSRI prescription and 10 pre-specified anomalies identified from the literature as associated with SSRI exposure[31]: CHD, severe CHD, neural tube defects, ano-rectal atresia/stenosis, renal dysplasia, craniosynostosis, hypospadias, including 3 anomalies associated with vasoconstriction (limb reduction, abdominal wall defects (gastroschisis and omphalocele) [55,56], and talipes equinovarus[37].
Abdominal wall defects (gastroschisis, Q792, omphalocele, Q793 and other wall defects, Q795) were combined to achieve sufficient numbers to report, considering their purported common aetiology (vasoconstriction of the omphalomesenteric artery) [58,59].

The composite outcomes, all major anomalies combined and major congenital anomalies or stillbirth, were based on the ICH (International Conference on Harmonisation) definition of serious adverse events[60].

Confounding

To minimise confounding by co-exposure, we achieved a relatively homogeneous population by excluding infants: 1) with EUROCAT coding[37] indicating known teratogenic syndromes (EUROCAT subgroups al82-84, al86) 2) exposed to medicines more closely associated with congenital anomalies than SSRIs during the 91 days either side of 1st day of LMP: anti-epileptic drugs (AEDs) (NO3)[61]; coumarins (B01AA), mainly warfarin[62]; insulins (A10A)[63]. We examined, but did not exclude, SSRI exposed cases for: 1) exposure to other potentially teratogenic prescription medicines 91 days either side of 1st day of LMP: systemic isotretinoin (D10BA); angiotensin converting enzyme inhibitors or angiotensin II blockers (C09); lithium (N05AN); benzodiazepines (N05BA); first generation antipsychotics (N05AA through N05AG); second generation antipsychotics (N05AH, N05AL, N05AX); carbimazole (H03BB); thyroxine (N03AA); medicines rarely prescribed in primary care but associated with anomalies: aminoglycosides, ergot derivatives, lindane, gold salts, penicillamine, methotrexate, chloroquine, radiopharmaceuticals[64]; 2) heavy alcohol use and substance misuse (Wales only); 3) maternal conditions indicating that the woman might not be considered to be from the normal healthy population: hospital admission for cancer; thyroid disorders; phenylketonuria; maternal congenital anomalies[65]; 4) maternal siblings with anomalies.

To explore confounding by indication (usually depressive illness [66]) we investigated whether women who discontinued prescriptions before the time when a biological effect would be expected (91 days before LMP) had similar risks to those receiving SSRI prescriptions during the vulnerable period (91 days either side of LMP). Those who discontinued were divided into those who did and did not resume prescriptions within a year of delivery. We defined:

• ‘paused SSRI exposure’ as ≥1 prescription during the 3–12 months before pregnancy plus ≥1 prescription during the year after pregnancy and no prescriptions during both the quarter preceding pregnancy and pregnancy.

• discontinuation (stopping) as ≥1 prescription during the 3–12 months before pregnancy and no further prescriptions throughout the quarter preceding pregnancy, pregnancy, and the first year after delivery.

As a sensitivity analysis, we repeated this analysis defining exposure as ≥1 prescription in each time period (1 year to 91 days before LMP, LMP ± 91 days, 1 year after delivery).

Statistical analysis

For each country separately, we explored associations between pre-specified outcomes (above) plus each congenital anomaly subgroup and all SSRIs, individual SSRIs, and all antidepressants. For exploration of individual SSRIs, those exposed to other SSRIs were excluded from the analysis. The odds of exposure for subjects with and without each anomaly were compared by calculating odds ratios (ORs) with Cornfield 95% confidence intervals (95% CI). For anomalies with >2 exposed cases in the 3 countries combined, meta-analysis of country-specific effects was undertaken, using the Mantel Haenszel method, with alternative continuity
corrections, described by Sweeting et al. (2004)[67]. Heterogeneity was assessed using the $I^2$
statistic. We repeated the analysis of all SSRIs excluding infants exposed to any non-SSRI anti-
depressants (e.g. SNRIs, tricyclic antidepressants); data availability restricted this to Norway &
Wales. When evaluating associations other than the 10 pre-specified signals, we applied Simes’
multiple testing procedure to control the false discovery rate to 5% (FDR) [68,69]. For ‘all
anomalies’, ‘anomalies + stillbirths’, CHD, and severe CHD, confounding by smoking and
socio-economic status were explored in separate fixed effects logistic regression models. The
SSRI dose-response relationships for all anomalies, CHD, severe CHD and ‘anomaly or still-
birth’ were explored for zero, ‘other’ and high doses, using random effects meta-regression.
Analyses were performed using Stata 12.1[70].

Wales sub-cohort
In Wales, confounding by indication was further explored by investigating depression and
unmedicated depression, defined as a diagnosis of depression in the woman’s record any time
during her registration with a participating GP before the end of the first trimester, but no
antidepressant prescribed in the 91 days either side of the 1st day of LMP. We explored associa-
tions between prespecified anomalies [31], and socioeconomic status (as Townsend fifth),
smoking, antipsychotics, substance misuse and heavy drinking and Down syndrom [71] in a
posteriori subgroups, to generate hypotheses for future work. Substance misuse often coincides
with heavy drinking, and vice versa, and we combined the two exposures. We took recorded
diagnoses of misuse at any time as indicative of a problem likely to recur. Analyses were under-
taken in SPSS version 20 for Windows[72].

Results
The population comprised 519,117 subjects (foetuses and infants): 346,739 from Norway;
56,447 from Funen, Denmark; 115,931 from Wales (Tables Aa-Ac in S1 Appendix, Fig 1). In
Wales, the included population were less deprived than the rest of Wales [41]. There were no
significant demographic differences between Funen County and ‘all Denmark’. Exposure to
SSRIs and antidepressants and prevalence of non-chromosomal, non-genetic congenital
anomalies were higher in Wales than the Scandinavian countries (Table 1). Norway had the
lowest prescription rates for paroxetine, >1 type of SSRI and high doses (Table 2).

The prevalence of major congenital anomalies was higher amongst those exposed to SSRI
prescriptions 91 days either side of 1st day of LMP (3.09%) than those unexposed (2.67%);
however, this was not statistically significant (OR 1.09, 0.99–1.21, Table 3). Exposure was sig-
ificantly associated with the composite adverse outcome ‘any major anomaly or stillbirth’
(OR 1.13, 1.03–1.24, [Table 3, number needed to harm [NNH] 192, 95% CI 118–512), severe
CHD (OR 1.50, 1.06–2.11, NNH 1094, 555–38,141), and abdominal wall defects (OR 1.75,
1.07–2.88, NNH 1629, 832–39,830).

We did not confirm associations between SSRIs and all CHD, neural tube defects, talipes
equinovarus, hypospadias, renal dysplasia, ano-rectal atresia/stenosis, limb reduction or cra-
niosynostosis. The association with gastroschisis did not reach statistical significance (OR 1.92,
0.97–3.78, based on 9 exposed cases, Table C in S1 Appendix). Non-significant positive associ-
tions involved all individual SSRIs, and included paroxetine with all CHD and ventricular
septal defect (VSD), fluoxetine with neural tube defects and citalopram with hypospadias. Esci-
talopram was associated with talipes equinovarus and abdominal wall defects (Tables Ba, C in
S1 Appendix). For all antidepressants, differences in prevalence of major anomalies between
exposed and unexposed were less marked and not statistically significant (OR 1.03, 0.93–1.13)
(Tables Bb, C in S1 Appendix). There were <3 exposed cases for 27/75 anomalies (Tables Ba,
Fig 1. Participant Flow diagram.

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Bb in S1 Appendix). When Simes’ False Discovery Rate procedure was applied, no associations reached the 5% false discovery rate significance level threshold, including those with diaphragmatic hernia and syndactyly (Table D in S1 Appendix). When data were re-analysed in Norway and Wales, with those co-prescribed other antidepressants excluded, prevalence rates and ORs changed little (Table C in S1 Appendix). Heterogeneity was low for most outcomes, except CHD and severe CHD (Table 3). The NNH for severe CHD varied: 298 (172–11,111) in Denmark, 854 (400–14,286) in Wales, and there was no association in Norway.

Dose-response
A minority were exposed to prescriptions for high doses of SSRIs (Table 2). Meta-regression for the 3 categories (high, other and zero dose) indicated significant associations for severe CHD and ‘anomaly or stillbirth’ and non-significant trends for all anomalies and CHD (Table 4). Denmark had a higher proportion of both high dose exposures and severe CHD.

Table 1. Summary of SSRI and antidepressant exposures and congenital anomaly (CA) prevalence in 3 countries: Denmark, Norway, Wales.

| Country  | Total Number | SSRI exposed³ LMP+/-91 days⁴ | Antidepressant exposed LMP+/-91 days |
|----------|-------------|-----------------------------|--------------------------------------|
|          | Pop (N)     | CA Cases (N) | Prevalence of CA (%) | Pop (N) | CA Cases (N) | % of population exposed | Prevalence of CA (%) | Pop (N) | CA Cases (N) | % of population exposed | Prevalence of CA (%) |
| Denmark  | 56,447      | 1288         | 2.28                   | 1169   | 33          | 2.07                  | 2.82                  | no data | no data |
| Norway   | 346,739     | 8991         | 2.59                   | 5451   | 149         | 1.57                  | 2.73                  | 7619    | 198         | 2.20                  | 2.60                  |
| Wales    | 115,931     | 3657         | 3.15                   | 6342   | 218         | 5.47                  | 3.44                  | 8019    | 264         | 6.92                  | 3.29                  |
| Total    | 519,117     | 13,936       | 2.68                   | 12,962 | 400         | 3.09                  | 3.09                  | 15,638  | 462         | 3.01                  | 2.95                  |

³Exposure defined as >0 prescriptions of SSRIs at any dose with or without co-prescriptions.
⁴LMP+/−91 days represents 91 days either side of 1st day of LMP.

Exclusions: 1) chromosomal, genetic, teratogenic anomalies; 2) exposure during the 91 days either side of LMP to: insulin, AEDs, coumarins.

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Table 2. SSRI exposure 91 days either side of LMP³ by individual SSRI⁵ and dose: 3 countries.

| Country  | Number exposed | % total exposed | Number exposed | % total exposed | Number exposed | % total exposed | Number exposed | % total exposed |
|----------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
|          | Denmar k       | Norway         | Wales          | Summed         |
| Population | 56,447         | 346,739        | 115,931        | 519,117        |
| Exposed to any SSRI | 1169          | 100           | 5451         | 100        | 6342         | 100        | 12,962       | 100          |
| SSRI     | Fluoxetine     | 155           | 13.26         | 509        | 9.34         | 1937        | 30.54        | 2601        | 20.07        |
|          | Citalopram     | 478           | 40.89         | 867        | 15.91        | 2683        | 42.31        | 4028        | 31.08        |
|          | Paroxetine     | 106           | 9.07          | 325        | 5.96         | 638         | 10.06        | 1069        | 8.25         |
|          | Sertraline     | 175           | 14.97         | 804        | 14.75        | 395         | 6.23         | 1374        | 10.60        |
|          | Escitalopram   | 138           | 11.80         | 2750       | 50.45        | 348         | 5.49         | 3236        | 24.97        |
| Exposed >1 SSRI | 117          | 10.01        | 196           | 3.60       | 341         | 5.38        | 654          | 5.05         |
| Dose     | High           | 255           | 21.81        | 364         | 6.68         | 810         | 12.77        | 1429        | 11.02        |
|          | Other          | 914           | 78.19        | 5087        | 93.32        | 5532        | 87.23        | 11,533      | 88.98        |

³Exclusions and exposures as Table 1.
⁵Fluvoxamine: 28 exposures and 0 exposed cases were identified, see Table Ba in S1 Appendix.

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Table 3. SSRI (NO6AB) exposures 91 days either side of LMP\textsuperscript{a} and outcomes\textsuperscript{b} based on signals: 3 countries.

|                      | Denmark       | Norway         | Wales          | Summed        | Meta-analysis |
|----------------------|---------------|----------------|----------------|---------------|---------------|
|                      | exposed n = 1169 | unexposed n = 55,278 | exposed n = 341,288 | exposed n = 6342 | Unexposed n = 109,589 | exposed n = 12962 | unexposed n = 506,155 | OR, 95% CIs | I\textsuperscript{2} |
| Anomaly or stillbirth | 40            | 3.42           | 1566           | 2.87          | 185           | 3.39          | 10412           | 3.05         | 248           | 3.91          | 3619           | 3.48         | 473           | 3.65          | 15039         | 3.13         | 1.13 (1.03–1.24) | 0 |
| All Anomalies        | 33            | 2.62           | 1255           | 2.27          | 149           | 2.73          | 8842           | 2.59         | 218           | 3.44          | 3439           | 3.14         | 400           | 3.09          | 13536         | 2.67         | 1.09 (0.99–1.21) | 0 |
| Neural Tube Defects  | <5            | 55             | 6              | 0.11          | 271           | 0.08          | 10             | 0.16         | 123           | 0.11          | 17–20          | 0.14         | 449           | 0.09          | 1.43 (0.89–2.30) | 0 |
| CHD                  | 16            | 1.37           | 447            | 0.81          | 44            | 0.81          | 3027           | 0.89         | 61            | 0.96          | 1029           | 0.94         | 121           | 0.93          | 4509          | 0.89         | 1.03 (0.86–1.24) | 56.66 |
| Severe CHD           | 6             | 0.51           | 98             | 0.18          | 9             | 0.21          | 567            | 0.17         | 19            | 0.30          | 200            | 0.18         | 34            | 0.26          | 865           | 0.17         | 1.50 (1.06–2.11) | 51.36 |
| Abdominal wall defects\textsuperscript{c} | <5            | 18–21          | 6              | 0.11          | 174           | 0.05          | 8              | 0.13         | 80            | 0.07          | 15–18          | 0.12         | 275           | 0.05         | 1.92 (1.13–3.24) | 0 |
| Talipes equinovarus \textsuperscript{c} | <5            | 73–76          | 12             | 0.22          | 473           | 0.14          | 11             | 0.17         | 190           | 0.17          | 24–27          | 0.19         | 736–9         | 0.15         | 1.20 (0.79–1.8) | 0 |
| Hypospadias          | <5            | 119–122        | 12             | 0.22          | 726           | 0.21          | 21             | 0.33         | 295           | 0.27          | 34–37          | 0.28         | 1140–1143     | 0.23         | 1.15 (0.82–1.61) | 0 |
| Ano-rectal atresia and stenosis\textsuperscript{d} | 7             | 0.06           | 150            | 0.03          | 1.85 (0.86–3.96) | 0 |
| Renal Dysplasia\textsuperscript{d} | 10            | 0.08           | 177            | 0.03          | 1.57 (0.83–2.98) | 0 |
| Limb reduction\textsuperscript{c, d} | 6             | 0.05           | 254            | 0.05          | 0.81 (0.36–1.82) | 0 |
| Craniosynostosis\textsuperscript{d} | 4             | 0.03           | 115            | 0.02          | 0.81 (0.3–2.21) | 0 |

We are unable to disclose numbers 1–4 from any single country. Accordingly, we are only able to supply ranges for related values. Where countries combined had <5 exposed cases we report only as an aggregate.

\textsuperscript{a}Exclusions and exposures as Table 1.

\textsuperscript{b}Anomalies selected for reporting based on background literature\textsuperscript{[31]}.

\textsuperscript{c}Anomalies associated with vasoconstriction\textsuperscript{[55]}.

\textsuperscript{d}Data from each country were analysed separately, but low numbers preclude reporting by country for these anomalies plus gastroschisis and omphalocele. Further information is in Table Ba, Bb (including numbers and % of cases), and Table C in S1 Appendix and EMC 2015 supplementary tables S3 and S4\textsuperscript{[41]}.

Analyses of SNRI exposure in Wales and Norway are in Table Bb and EMC (2015)\textsuperscript{[41]} (Denmark was unable to supply data on SNRIs). There were 1448 SNRI exposures and 46 exposed cases (3.18%) (OR 1.14, 0.85–1.53). No associations with anomalies listed above where 95% confidence intervals did not include one were identified. Emboldened text indicates 95% confidence intervals exclude 1.

CHD represents congenital heart defect.

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Confounding by co-exposure

Adjusting for smoking and SES made little difference to ORs. Adjusting for smoking reduced the numbers of exposed cases, due to missing data disproportionately affecting the cases (Table Aa in S1 Appendix) and uncertainty over ex-smokers, and hence widened confidence intervals (Table 5). Checks indicated that: 52 of the 400 exposed cases had been exposed to prescription medicines identified as potentially teratogenic (listed under ‘confounding’), benzodiazepines (21), thyroxine (13), antipsychotics first generation (9), second generation (5), angiotensin converting enzyme inhibitors (3), lithium (1), and 0 for all other exposures; 30 were exposed to maternal ill-health; 14 had siblings in the dataset with anomalies, and 12 had mothers with an anomaly recorded. Of the 34 exposed severe CHD cases, 6 were also exposed to potential teratogens of varying potency, benzodiazepines (2 or <5), thyroxine (2), lithium (1), and first generation antipsychotics (1), 2 were exposed to maternal ill-health and none had maternal siblings or mothers with any congenital anomaly.

Table 4. High Dose exposure and ‘all anomalies’, CHD, severe CHD, ‘Stillbirth or Anomaly’: 3 countries.

|                          | High dose LMP±91 days n = 1429 | Other dose LMP±91 days n = 11,533 | Unexposed LMP±91 days n = 506,155 | Meta regressionb |
|--------------------------|---------------------------------|-----------------------------------|-----------------------------------|------------------|
|                          | N % of exposed                  | N % of exposed                    | N % of exposed                    | OR (95%CI)       |
| Anomaly or stillbirth    | 53 3.71                         | 420 3.64                         | 15,829 3.13                      | 1.10 (1.02–1.20) |
| All anomalies            | 43 3.01                         | 357 3.10                         | 13,525 2.67                      | 1.08 (0.99–1.17) |
| CHD                      | 18 1.26                         | 103 0.89                         | 4495 0.89                        |                  |
| Severe CHD               | 7 0.49                          | 27 0.23                          | 864 0.17                        | 1.49 (1.13–1.97) |

Exclusions and exposures as Table 1.

Table 5. Congenital anomalies and stillbirths and SSRI exposure LMP±91 days: analyses adjusted for smoking and socio-economic status (SES).

|                          | Adjusted analysis | Unadjusted analysis | Number of exposed cases |
|--------------------------|-------------------|---------------------|-------------------------|
|                          | Meta OR (95% CI)  | I²                  | Meta OR (95% CI)        | I²                  |
| Outcome adjusted for smoking |                    |                     |                        |                     |
| All Anomalies            | 1.08 (0.97–1.20)  | 0                   | 1.09 (0.99–1.21)        | 0                   |
| CHD                      | 1.00 (0.82–1.21)  | 46.4                | 1.03 (0.86–1.24)        | 55.66               |
| Severe CHD               | 1.43 (0.99–2.07)  | 47.9                | 1.50 (1.06–2.11)        | 51.36               |
| Anomaly or stillbirth    | 1.12 (1.01–1.23)  | 0                   | 1.13 (1.03–1.24)        | 0                   |
| Outcome adjusted for SESb: lowest vs. the rest |                    |                     |                        |                     |
| All Anomalies            | 1.09 (0.98–1.21)  | 0                   | 1.09 (0.99–1.21)        | 0                   |
| CHD                      | 1.03 (0.85–1.23)  | 25.1                | 1.03 (0.86–1.24)        | 55.66               |
| Severe CHD               | 1.47 (1.04–2.08)  | 23.6                | 1.50 (1.06–2.11)        | 51.36               |
| Anomaly or stillbirth    | 1.12 (1.02–1.23)  | 0                   | 1.13 (1.03–1.24)        | 0                   |

Exclusions and exposures as Table 1.

bSES: years in education in Denmark and Norway and Townsend fifth in Wales (Tables Aa-c in S1 Appendix).

When SES was examined as a linear trend, results were essentially unchanged. The decision to compare the most deprived with the rest was based on data in Tables E, F in S1 Appendix.

Numbers were too low for adjusted analyses in some anomalies of interest, including abdominal wall defects. In Wales, abdominal wall defects and SSRI exposure were associated with smoking and SES (Table F in S1 Appendix).

Unadjusted analyses are reproduced here for the convenience of readers.

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Confounding by indication

a) Exposure patterns. Including only women present in the database from 1 year before to 1 year after pregnancy reduced the population (Fig 1), but left prevalence of anomalies and SSRI exposure largely unchanged. Prevalence appeared lowest in those never exposed, increasing in stoppers, pausers and those exposed during pregnancy, but differences were not statistically significant. The prevalence of severe CHD appeared lower (0.23%) in those prescribed ≥1 SSRI prescription(s) in the 91 days either side of LMP than those receiving >1 prescription (0.31%) (Table 6 and Table G in S1 Appendix).

b) Depression in Wales. For women present on the database during pregnancy and 1 year either side (n = 103,204), a recorded diagnosis of depression (ever) was not associated with increased prevalence of all anomalies (OR 1.01, 0.91–1.12, Table 7 and Table H in S1 Appendix). The prevalence of anomalies amongst those with a diagnosis of depression, medicated (3.22%) or unmedicated (3.19%) (Table H in S1 Appendix), was slightly lower than following SSRI exposure, regardless of diagnosis (3.44%) (Table 1), but such differences were not statistically significant. More infants exposed to medicated than unmedicated depression had severe CHD (OR 1.60, 0.70–3.66), but numbers were low (Table 7 and Table H in S1 Appendix).

Deprivation was associated with depression and SSRI prescription (Table E in S1 Appendix). We found no significant associations between all anomalies, ‘anomalies and stillbirths’, CHD, severe CHD and: smoking, substance misuse or heavy drinking, antipsychotics or deprivation. Abdominal wall defects were associated with deprivation and smoking (Table F in S1 Appendix).

In subgroups of women in Wales recorded (ever) as heavy drinkers or substance misusers, the most deprived fifth, those prescribed antipsychotics within 91 days of LMP, and smokers, additional SSRI exposure appeared to increase the prevalence of congenital anomalies (Table 8).

### Table 6. Comparisons of stopping before pregnancy, pausing during pregnancy, exposure LMP±91 days*, and unexposed for 11 quartersb for all anomalies, CHD and severe CHD, including receipt of >0 and >1 prescriptions: 3 countries.

|                          | Exposed >0 SSRI prescription n = 11,512 | Exposed >1 SSRI prescription n = 6392 |
|--------------------------|----------------------------------------|--------------------------------------|
|                          | Unexposed 11 quartersb                  | Stoppers                             | Pausers                             | Exposed LMP±91 days |
|                          | N           | %          | N           | %          | N           | %          | n           | %          |
| Total                    | 426,962     |            | 6315        |            | 2203        |            | 11,512      |            |
| All anomalies            | 11,049      | 2.59%      | 175         | 2.77%      | 62          | 2.81%      | 341         | 2.96%      |
| CHD                      | 3651        | 0.82%      | 64          | 1.01%      | 24          | 1.09%      | 94          | 0.82%      |
| Severe CHD               | 722         | 0.16%      | 9           | 0.14%      | 4           | 0.18%      | 26          | 0.23%      |
| Exposed >1 SSRI prescription n = 6392 |
|                          | Unexposed 11 quartersb                  | Stoppers                             | Pausers                             | Exposed LMP±91 days |
|                          | N           | %          | N           | %          | N           | %          | n           | %          |
| Total                    | 426,962     |            | 3146        |            | 923         |            | 6392        |            |
| All anomalies            | 11,049      | 2.59%      | 87          | 2.77%      | 26          | 2.82%      | 190         | 2.97%      |
| CHD                      | 3651        | 0.82%      | 29          | 0.92%      | 11          | 1.19%      | 56          | 0.88%      |
| Severe CHD               | 722         | 0.16%      | 6           | 0.19%      | 3           | 0.33%      | 20          | 0.31%      |

*Exclusions as Table 1 plus ‘not on database for 1 year either side of pregnancy’.

b11 quarters—pregnancy and 1 year either side.

A full version of this table, with ORs and 95% CIs is available in Table G in S1 Appendix. For all anomalies and severe CHD, differences between exposed to >1 SSRI prescription and unexposed yielded 95% confidence intervals excluding one.

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Congenital anomalies appeared more prevalent amongst infants exposed than unexposed to prescription of SSRIs within 91 days of 1st day of LMP, consistent with recent meta-analyses [26,30,73]; this difference was not statistically significant. However, the increase was significant for the composite adverse outcome of ‘anomaly or stillbirth’ (OR 1.13, 1.03–1.24, NNH 192). Significant dose-response relationships were found between SSRI prescription and ‘anomaly or stillbirth’ and severe CHD (meta-regression ORs 1.10, 1.02–1.20, and 1.49, 1.12–1.97), supporting work on paroxetine[34] and umbilical cord samples[74], but contrary to reports with fewer exposed cases[15], and different classifications[32].

The literature’s inconsistency regarding SSRIs and CHD is reflected in our incongruent findings for all CHD and severe CHD. The dose-response association between SSRI prescription and severe CHD (Table 4) appears stronger than for all CHD, but there is insufficient power to test this hypothesis. The association with severe CHD supports some studies [15,30,31], while the absence of association with all CHD reflects others[22,29,32,33], suggesting that SSRIs may only affect certain cardiac anomalies. As elsewhere, paroxetine was associated with all CHD and VSD[26,31,33], possibly attributable to its saturation kinetics[47]. Some previously reported associations were confined to a single SSRI: neural tube defects [33,35] with fluoxetine (OR 2.57, 1.21–5.46), escitalopram with talipes equinovarus[52], citalopram with hypospadias [27,75] (Table C in S1 Appendix). Genetic variation[76] and induction of the cytochrome P450 system, essential for SSRI metabolism, which occurs early in pregnancy, may reduce SSRI bioavailability and mitigate any adverse impact[51,77], particularly at standard doses.

Depression and social stressors are associated with activation of the hypothalamic-pituitary-adrenal (HPA) axis, pro-inflammatory cytokines[78], and placental equivalents[79].

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**Table 7. Depression, medicated and unmedicated and congenital anomalies and stillbirths in Wales.**

| Anomaly or stillbirth | Depression exposed to N06AB LMP91 days n = 2897 | Depression unmedicated with N06AB LMP91 days n = 10292 |
|-----------------------|-----------------------------------------------|------------------------------------------------------|
| Population            | Population                                    | Population                                           |
| N                     | % of diagnosed depressed                      | % of exposed                                         |
| an050 Gastrostchisis  | 11                                            | 0.08                                                |
| aL54 Renal dysplasia  | 9                                             | 0.07                                                |
| aL59 Hypospadias      | 34                                            | 0.26                                                |
| aL61 Limb reduction   | 7                                             | 0.05                                                |
| aL66 Talipes equinovarus | 23                                        | 0.17                                                |
| al101: Oro-facial clefts | 17                                         | 0.12                                                |

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**Discussion**

Congenital anomalies appeared more prevalent amongst infants exposed than unexposed to prescription of SSRIs within 91 days of 1st day of LMP, consistent with recent meta-analyses [26,30,73]; this difference was not statistically significant. However, the increase was significant for the composite adverse outcome of ‘anomaly or stillbirth’ (OR 1.13, 1.03–1.24, NNH 192). Significant dose-response relationships were found between SSRI prescription and ‘anomaly or stillbirth’ and severe CHD (meta-regression ORs 1.10, 1.02–1.20, and 1.49, 1.12–1.97), supporting work on paroxetine[34] and umbilical cord samples[74], but contrary to reports with fewer exposed cases[15], and different classifications[32].

The literature’s inconsistency regarding SSRIs and CHD is reflected in our incongruent findings for all CHD and severe CHD. The dose-response association between SSRI prescription and severe CHD (Table 4) appears stronger than for all CHD, but there is insufficient power to test this hypothesis. The association with severe CHD supports some studies [15,30,31], while the absence of association with all CHD reflects others[22,29,32,33], suggesting that SSRIs may only affect certain cardiac anomalies. As elsewhere, paroxetine was associated with all CHD and VSD[26,31,33], possibly attributable to its saturation kinetics[47]. Some previously reported associations were confined to a single SSRI: neural tube defects [33,35] with fluoxetine (OR 2.57, 1.21–5.46), escitalopram with talipes equinovarus[52], citalopram with hypospadias [27,75] (Table C in S1 Appendix). Genetic variation[76] and induction of the cytochrome P450 system, essential for SSRI metabolism, which occurs early in pregnancy, may reduce SSRI bioavailability and mitigate any adverse impact[51,77], particularly at standard doses.

Depression and social stressors are associated with activation of the hypothalamic-pituitary-adrenal (HPA) axis, pro-inflammatory cytokines[78], and placental equivalents[79].
which affect organogenesis[80], foetal growth[81], and birth outcome[82]. We found no association between anomalies linked with maternal social stressors (oro-facial clefts)[83] and SSRIs, antidepressants or depression (Table 7 and Tables C, H in S1 Appendix). This intimates that independent serotoninergic[11] and vasoconstrictor[9,50] mechanisms might underlie adverse outcomes following SSRI exposure[84]. SSRI-induced vasoconstriction[9,51] may explain associations between SSRIs and low birth weight, growth restriction[85–87], and persistent pulmonary hypertension[88], contributing to synergy in our composite adverse outcome. (Growth restriction accounts for 43% of stillbirths[89]). Stillbirth is a relatively rare outcome (prevalence <0.5%), not previously associated with SSRI exposure[90,91].

Table 8. Subgroup explorations in Wales: SSRI exposure and congenital anomalies or Stillbirths. a

| SSRI exposure 91 days either side of LMP | OR (95%CI) where available |
|-----------------------------------------|---------------------------|
| SSRI exposed LMP±91 days n (% exposed) | Not SSRI exposed LMP±91 days n (% not exposed) |
| Heavy drinking or substance misuse recorded (n = 1658) | |
| Number | 288 | 1370 |
| All Anomalies | 18 (6.3) | 38 (2.8) | 2.34 (1.31–4.16) |
| CHD | 6 (2.1) | 13 (0.9) | 2.22 (0.85–5.89) |
| Severe CHD | <5 | <5 |
| Anomaly or stillbirth | 19–22 (6.6–7.6) | 44 (3.2) | >1 (<0.05) |
| Most deprived fifth (Townsend index of material deprivation) (n = 25,763) | |
| Number | 1910 | 23,853 |
| All Anomalies | 70 (3.7) | 781 (3.3) | 1.12 (0.88–1.44) |
| CHD | 19 (1.8) | 235 (1.0) | 1.01 (0.63–1.62) |
| Severe CHD | 5 (0.3) | 47 (0.2) | 1.33 (0.53–3.35) |
| Anomaly or stillbirth | 75 (3.9) | 870 (3.6) | 1.08 (0.85–1.37) |
| Exposed to any antipsychotic b at any time (n = 833) | |
| Number | 266 | 567 |
| All Anomalies | 9/266 (3.4) | 16/567 (2.8) | 1.21 (0.53–2.77) |
| CHD | <5 |
| Severe CHD | <5 |
| Anomaly or stillbirth | 10–13 (3.8–4.9) | 17–21 (3.0–3.7) |
| Smokers c (n = 30,534) | |
| Number | 2583 | 27,951 |
| All Anomalies | 92/2583 (3.6) | 904/27,951 (3.2) | 1.11 (0.89–1.38) |
| CHD | 23/2583 (0.89) | 265/27,951 (0.9) | 0.94 (0.61–1.44) |
| Severe CHD | 7/2583 (0.27) | 49/27,951 (0.2) | 1.55 (0.70–3.42) |
| Anomaly or stillbirth | 110/2583 (4.3) | 1019/27,951 (3.6) | 1.18 (0.96–1.44) |

aExclusions and exposures as Table 7.
bFor antipsychotic and benzodiazepine exposure see Table F in S1 Appendix.
cAlthough smoking was well recorded, some 15% women were classified as ex-smokers, with no cessation date; fieldwork experience indicates that some women self-report their smoking status as ‘ex’ when discontinuation has been <24 hours.

Amongst the 110 live birth cases of Down syndrome, exposure to SSRIs increased the incidence of CHD from 60/101 (60%) to 9/9 (100%) (RR 1.68, 1.43–1.98).

Abdominal wall defects: too few cases to report.

Recorded recreational drug use was implausibly low, and not analysed.
Adjusting for smoking and SES left findings largely unchanged (Table 5), as elsewhere [16,28]. Exploration in Wales found no evidence for major confounding, except for abdominal wall defects (Table F in S1 Appendix). Excluding subjects exposed to insulin, AEDs and coumarins reduced the need to adjust for co-exposure[32]. SSRI prescription conferred additional risks on those co-exposed to substance misuse or heavy drinking or other psychoactive medicines[17,92–95] (Table 8).

To disentangle SSRI exposure from depression, like others [15], we compared those exposed to SSRIs with those where prescriptions had been stopped or paused. Although prevalence of ‘all anomalies’ and severe CHD was lower in those who stopped rather than continued prescriptions, confidence intervals were wide, indicating limited power of this analysis and the presence of confounding (Table 6 and Table G in S1 Appendix). In Wales, we analysed ‘any record of depression’, based on practitioners’ reluctance to repeat data entries and the ‘depression diathesis model’, which suggests that any episode may predispose to stressor-induced release of pro-inflammatory cytokines, permanently altering hippocampal, prefrontal and frontocingulate neurochemistry and connections[78]. We found no associations between depression and anomalies (Table 7 and Table H in S1 Appendix), supporting suggestions that depression and antidepressants may act separately[84,96] in modifying release of pro-inflammatory cytokines that affect organogenesis. Similarly, meta-analysis indicates that increased risks of preterm birth persist when SSRI exposed are compared with unmedicated controls diagnosed with depression [97]. Our definition of depression (any record, ever) may contribute to incongruence with other reports[22,98]. We acknowledge that prescription or resumption or higher doses of SSRIs may indicate on-going, recurrent or more severe depression, compounding the difficulties of disentangling the effects of prescriptions from underlying illness.

**Strengths and limitations**

Findings are strengthened by: precise diagnostic coding of congenital anomalies [37]; inclusion of TOPFA cases and stillbirths; contemporary controls; accounting for exposure to other antidepressants and SES; prospective data[99], free from recall bias [100]: these may explain differences with the published literature [15,16,24,32,33]. Most infants exposed to SSRIs in early pregnancy were not exposed in late pregnancy [3], reducing any over-ascertainment of anomalies in neonatal assessments of ‘high risk’ infants: the main concern is conflation of ASD with patent foramen ovale, which is precluded by EUROCAT coding [37]. Where associations were observed, effects were modest (ORs below 2), and the low numbers of exposed cases necessitate cautious interpretation, but the associations with severe CHD and ‘major anomaly or stillbirth’ are strengthened by dose-response relationships[101]. **Generalization** of findings on ‘all anomalies’, with or without stillbirths is strengthened by consistency across different populations ($I^2 = 0$ for both analyses) (Table 3 and Table C in S1 Appendix). Our findings are limited by: dilution of exposure; incomplete recording in electronic databases; and study size.

Our **effect sizes** may be conservative and ORs diluted by our extended exposure window, and threats to prescription adherence. Our extended time window before LMP (91 days) was based on typical prescription duration and pharmacokinetic parameters, which differ between SSRIs. We acknowledge that this may have led to some unexposed subjects being misclassified as exposed, diluting ORs [102], particularly for SSRIs with shorter half-lives (citalopram, sertraline, escitalopram, and low dose paroxetine)[47], possibly explaining divergent findings [16,32,103].

**Adherence to prescribed regimens** cannot be ascertained from prescription or dispensing data. However, it is more likely where >1 prescription is issued, and therefore our stronger
findings when analysing women exposed to >1 prescription are consistent with dilution due to exposure misclassification from non-adherence. International differences in exposure observed may, in part, reflect differences in issued (Wales) versus redeemed (Norway, Denmark) prescriptions. Prescription non-redemption varies between settings; reviewers suggest a mean of 16.4% (range 11–19%) [104]. For antidepressants, estimates range from 20% in the USA where affordability is a prominent concern [105], to 4% in the Netherlands [106] and 4.5% (CNS medicines) in UK primary care [107].

Electronic cohorts based on prospectively collected routine data facilitate pharmacovigilance across whole populations; however, clinical details (other than EUROCAT coding) including indications for prescriptions and severity of illness, confounding variables and genotype may be incompletely recorded. Dose-response explorations were based on tablet size, and we were unable to take account of formulation or number of tablets or packets prescribed. Genetic vulnerability to environmental factors, including SSRIs, is hypothesised [76], but rarely recorded. Some anomalies, including some not associated with recognised syndromes, can result from inherited conditions [108]. However, family histories tend to be incompletely recorded, and there may be no information on fathers and other family members, including any paternal half-siblings. Information on paternity is also difficult to obtain in fieldwork [109]. CHDs are associated with maternal CHD [65], and even a small number of affected women might affect our interpretation of the severe CHD outcome. Although we checked as thoroughly as possible, data on maternal morbidities were limited by timeframes of databases and, possibly, incomplete recording. We did not exclude women with: diabetes not prescribed insulin, unmedicated epilepsy, glucose-6-phosphate dehydrogenase deficiency, sickle cell anaemia, maternal hypertension. BMI was poorly recorded in all databases, precluding exploration of confounding by obesity [110].

Recreational drug use, heavy alcohol use and substance misuse are captured poorly in clinical care, fieldwork and databases. These potential confounders were not available in the Scandinavian databases. Only problems recorded by primary care professionals could be identified in Wales; this would not include casual users or regular users not reporting problems. Depression may be under-reported in primary care records, due to inaccurate diagnosis by primary care practitioners [111], fears of ‘labeling’ or stigmatizing [112], and, possibly, incomplete record transfer from secondary care. Accordingly, we acknowledge the risks of under-ascertainment, and the limitations of taking the absence of any records as indicative of non-exposure. Adjustment was limited by low numbers of exposed cases, incomplete recording of smoking (Table 6 and Tables Aa-c, G in S1 Appendix) and, in Denmark, a higher prevalence of missing data amongst cases (Tables Aa-c in S1 Appendix). However, in Wales, alternative predictors were not identified for anomalies other than abdominal wall defects (Table F in S1 Appendix).

Analyses of all antidepressants and SSRIs excluding co-prescription of other antidepressants could not include Denmark, and therefore are not directly comparable to the main results.

The study’s size was sufficient (>312,000) to detect an association between SSRI exposure (2.50%) with major anomalies (prevalence 2.68%, Table 1) greater than OR 1.2, with 80% power and alpha 0.05, but >1,000,000 subjects would be needed to detect ORs of 1.1. For the commonest anomaly, CHD (prevalence 0.9%) and the commonest SSRI (citalopram, 0.8% exposure), there were sufficient subjects (>456,000) to detect an OR of 1.5 [113]. Higher prescription rates in Wales gave more exposed pregnancies (and power) than previous cohorts [14,21] benefitting from verified EUROCAT coding [15,22,33].

We acknowledge the hazards of multiple testing, without correction, but recognise the tensions between umbrella terms, which can hide true signals between specific anomalies and
specific medicines, and narrow categories or rare outcomes yielding numbers too small for statistical comparisons[114,115]. A priori hypotheses[9,27,31,35,51] were tested without statistical adjustment, to limit misinterpretation (Table 3)[116]. Associations between individual agents and anomalies offer signals for replication in independent data sets (Table C in S1 Appendix). Our population-based cohort study yielded lower ORs than Wemakor et al.’s[31] case-malformed control study of 12 EUROCAT registries, suggesting that we have not over-estimated harms, congruent with reports that estimates of adverse event rates are lower in cohort than case-control studies[117].

Logical and biological inferences should be considered when interpreting these findings, which are congruent with seven of the nine Bradford-Hill criteria of causation [118]: temporal and dose-response relationships; consistency of effect size (ORs) for ‘all anomalies’ internally, and with the literature[26,30,73]; biological plausibility; consideration of alternative explanations (depression, SES, smoking); specificity to severe CHD; and coherence with extant theories of serotonergic transmission and vasoconstriction. However, neither we nor others offer experimental evidence, and the associations, while persistent and clinically serious [60], represent small absolute risk differences (Table 3). Where partial overlap between our data and that published by EUROCAT[31], the Danish 1995–2008[103], and Nordic authors 1996–2010[16] occurs, findings are consistent. However, the last excluded stillbirths and TOPFAs, reducing the prevalence of anomalies. We have avoided P values, but acknowledge the problems inherent in dichotomizing data according to 95% confidence intervals where assignment is not randomized and assumptions (for example on adherence) are unverifiable [119]: interpretation and translation into clinical practice rest with readers.

### Interpretation and care pathways

Our findings resonate with larger cohorts and meta-analyses[26],[30],[73], despite the risks of attenuation of odds ratios, above. SSRI prescription in the 91 days either side of LMP was associated with higher prevalence of anomalies and stillbirths: ~7 rather than ~6 adverse outcomes per 200 exposed births. The heterogeneity in severe CHD may be attributable to diverse prescription regimens, environmental factors or ill-defined contextual variables. The higher prevalence was most apparent in Denmark, where single prescriptions were unusual and high doses relatively common, and absent in Norway, where single prescriptions were more common, high doses and paroxetine relatively rare, and escitalopram the most popular SSRI. The UK formulary [120] notes the pro-arrhythmic potential of escitalopram and contra-indicates breastfeeding, which may explain lower use in Wales.

Antidepressant use in pregnancy is determined by the balance between benefits to the woman and harms to the foetus: there is no certainty that realisation of the fourth (reducing child mortality) and fifth (improving maternal health) UN Millennium Development goals [121] will always coincide. Congenital anomalies and stillbirths are not the only harms associated with antidepressants[122]. Prescribing decisions are informed by other possible harms [73,123]: spontaneous abortion[29,124], low birth weight, prematurity, admission to neonatal special care facilities [33,85–87,125], gestational hypertension, postpartum haemorrhage[126], persistent pulmonary hypertension in neonates[88,120,127,128], concerns over delayed motor development[129].

The uncertain clinical effectiveness of antidepressants in pregnancy[126,130] for mild or moderate depression[131,132], treatment resistance in some 30% patients[78], contra-indication in mild depression [120], and wide variations in prescribing across Europe[3] underlie recommendations to restrict pharmacotherapy in pregnancy to women with severe depression [133–135] or adjust prescribing thresholds[73]. However, poor parental perinatal mental
health can adversely affect childhood outcomes [136], while effects on perinatal outcomes are modest [137], and more marked in developing countries [138]. Guidelines’ equivocation places the onus on prescribers [139,140], despite constraints in primary care, including short appointment times[141]. Withholding or withdrawing antidepressants from women with serious illness may worsen illness or induce withdrawal symptoms or relapse[133,142], and clinicians are mindful of the increased risk of harm, including suicide, in the 28 days following discontinuation[143], but more evidence relating to those less seriously ill is needed. The higher exposure rates in Wales, compared with Norway and Denmark, plus the low prevalence of mental health diagnoses [66], may suggest that women in Wales suffering less severe depression are more likely to be prescribed SSRIs. These women may derive less benefit from antidepressants, whilst risking the same harms.

Implications

The clinical importance of stillbirth and major congenital anomalies, including severe CHD, suggests that small increases in absolute risk might influence decisions on therapy and care pathways at population level[144]. Examination of three Northern European population cohorts consistently indicated an association between SSRIs and major anomalies, which increased when stillbirths were included. Uniquely, the association identified with severe CHD was supported by: a dose-response relationship, lower prevalence in those stopping SSRIs, higher prevalence in those with >1 prescription, minimal confounding by SES, plus, in Wales, no association with alternative exposures, including depression. Given the rarity of specific congenital anomalies and ethical considerations, randomised trials with these outcomes may never be undertaken. However, since risk estimates for adverse events are similar in trials and observational studies[145], these findings have implications for practice.

Even if associations reported here are not necessarily causal, SSRI prescriptions can be identified in primary care records and offer convenient markers for increased vulnerability, more easily ascertained and reliable than smoking status or recreational drug consumption [109,146]. Balancing the number needed to harm, 192, with the severity of potential adverse effects (stillbirth or major anomaly) [53], whilst minimising any iatrogenic harm [140] might entail regarding records of SSRI prescriptions as indication to:

- Target all women contacting primary care for SSRI prescriptions, not just those identifying themselves as planning pregnancy, since ~43% UK pregnancies are unplanned[147].
- Regard substance misuse or heavy drinking as possible indicators of high risk from SSRI prescribing (6.3%).
- Expand pre-conception care to include: reviewing therapeutic regimens, particularly high doses of SSRIs; reflecting that ~40% women discontinuing SSRIs after conception do not restart within a year of childbirth [3], and cognitive behavioural therapy may be equally effective[148]; prescribing folic acid, which may reduce the prevalence of CHD[149].
- Consider offering women prescribed SSRIs in pregnancy third trimester scans or alternative continuous monitoring technology to:
  - take advantage of advances in monitoring and surgery in utero
  - ensure appropriate levels of neonatal care are available at birth.
- Consider whether there is now sufficient evidence and clinical indication to offer a modified care pathway to include detailed ultrasound scans with views of the 4 cardiac chambers, outflow tracts and aortic arch plus Doppler investigation of blood flow [150], even if
not otherwise indicated. Ultrasound is not considered to be associated with risk, and there are no reported harms [151], with follow up to age 15–16 [152]; some may consider that the injunction “Do no harm” [140] might justify the additional clinical work, and any additional anxiety for parents associated with clinically unimportant incidental findings.

Supporting Information

S1 Appendix. Supplementary tables. Tables Aa-c. The populations. Tables Ba and Bb. Anomalies and exposures for each SSRI and all antidepressants. Table C. Anomalies and SSRI exposure for each agent with data from 3 countries. Table D. Anomalies and SSRI exposure with and without antidepressants. Table E. Deprivation and selected exposures in Wales. Table F. Exploration of anomalies and alternative exposures in Wales. Table G. Comparisons of stopping before pregnancy, pausing during pregnancy, exposure LMP±91 days, and unexposed for 11 quarters for all anomalies, CHD and severe CHD, including receipt of >0 and >1 prescriptions: 3 countries. Table H. Depression, medicated and unmedicated and congenital anomalies and stillbirths in Wales.

S2 Appendix. STROBE statement.

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Details of ethics’ committees’ approvals

Wales. This study uses anonymised data held in the Secure Anonymised Information Linkage (SAIL) system, which is part of the national e-health records research infrastructure for Wales. We should like to acknowledge all the data providers who make anonymised data available for research. Data held in SAIL databases are anonymised and aggregated and have been obtained with permission of relevant Data Protection Officers, as approved by the National Research Ethics Service, Wales. EUROmediCAT was approved by the SAIL Information Governance Review Panel (IGFRP) on 24th March 2011. Since EUROmediCAT uses only anonymised data, ethical review was deemed unnecessary.

Norway. The EUROmediCAT project was given approval from the Norwegian Data Inspectorate on 12th February 2013 (12/00617-4/EOL), and from the Ethical Committee for Research on 5th June 2012 and 7th July 2015 (2012/757/REK nord).

Funen, Denmark. Linkage of databases for the EUROmediCAT project was approved by the Danish Data Inspection Agency on May 27th 2011 (2011-231-0098).

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**References**

1. Peters P, Miller R, Schaefer C. General commentary on drug therapy and drug risks in pregnancy. Pp.1–23 In: Schaefer C, Peters P, Miller R. (eds) Drugs During Pregnancy and Lactation. 2015; Academic Press/ Elsevier, London 3rd edition.

2. Alwan S, Reefhuis J, Rasmussen SA, Friedman JM, Study NBDP. Patterns of antidepressant medication use among pregnant women in a United States population. J Clin Pharmacol. 2011; 51(2):264–70. doi: 10.1177/0091270010373928 PMID: 20683997.

3. Chartton RA, Jordan S, Pierini A, Garne E, Neville AJ, Hansen AV, et al. Selective serotonin reuptake inhibitor prescribing before, during and after pregnancy: a population-based study in six European regions. BJOG. 2015; 122(7):1010–20. doi: 10.1111/1471-0528.13143 PMID: 25952424.

4. Olivier JD, Akerud H, Kahlola H, Pawluski JL, Skalkidou A, Högberg U, et al. The effects of maternal depression and maternal selective serotonin reuptake inhibitor exposure on offspring. Front Cell Neurosci. 2013; 7:73. doi: 10.3389/fncel.2013.00073 PMID: 23734100.

5. Laine K, Heikkinen T, Ekblad U, Kero P. Effects of exposure to selective serotonin reuptake inhibitors during pregnancy on serotonergic symptoms in newborns and cord blood monoamine and prolactin concentrations. Arch Gen Psychiatry. 2003 Jul; 60(7):720–6. doi: 10.1001/archpsyc.60.7.720 PMID: 12860778.

6. Salisbury AL, Ponder KL, Padbury JF, Lester BM. Fetal effects of psychoactive drugs. Clin Perinatol. 2009; 36(3):595–619. doi: 10.1016/j.cjp.2009.06.002 PMID: 19732616.

7. Daws LC, Gould GG. Ontogeny and regulation of the serotonin transporter: providing insights into human disorders. Pharmacol Ther. 2011; 131(1):61–79. doi: 10.1016/j.pharmthera.2011.03.013 PMID: 21447358.

8. Santos-Silva AJ, Cairrão E, Marques B, Verde I. Regulation of human umbilical artery contractility by different serotonin and histamine receptors. Reprod Sci. 2009; 16(12):1175–85. doi: 10.1177/1933719109343787 PMID: 19801536.

9. Ray S, Stowe ZN. The use of antidepressant medication in pregnancy. Best Pract Res Clin Obstet Gynaecol. 2014; 28(1):71–83. doi: 10.1016/j.bpobgyn.2013.09.005 PMID: 24211026.

10. Sadler TW. Selective serotonin reuptake inhibitors (SSRIs) and heart defects: potential mechanisms for the observed associations. Reprod Toxicol. 2011; 32(4):484–9. doi: 10.1016/j.reprotox.2011.09.004 PMID: 21963886.

11. Velasquez JC, Goeden N, Bonnin A. Placental serotonin: implications for the developmental effects of SSRIs and maternal depression. Front Cell Neurosci. 2013; 7:73. doi: 10.3389/fncel.2013.00047 PMID: 23630464.

12. Chambers CD, Johnson KA, Dick LM, Felix RJ, Jones KL. Birth outcomes in pregnant women taking fluoxetine. N Engl J Med. 1996; 335(14):1010–5. doi: 10.1056/NEJM19961003351402 PMID: 8793924.

13. Wogelius P, Nørgaard M, Gislum M, Pedersen L, Schneehyder HC, Sørensen HT. Further analysis of the risk of adverse birth outcome after maternal use of fluoroquinolones. Int J Antimicrob Agents. 2005; 26(3):323–6. doi: 10.1016/j.ijantimicag.2005.06.017 PMID: 16144758.

14. Kornum JB, Nielsen RB, Pedersen L, Mortensen PB, Nørgaard M. Use of selective serotonin-reuptake inhibitors during early pregnancy and risk of congenital malformations: updated analysis. Clin Epidemiol. 2010; 2:29–36. PMID: 20865100.

15. Jimenez-Solem E, Andersen JT, Petersen M, Broedbaek K, Jensen JK, Afzal S, et al. Exposure to selective serotonin reuptake inhibitors and the risk of congenital malformations: a nationwide cohort study. BMJ Open. 2012; 2(3). doi: 10.1136/bmjopen-2012-001148 PMID: 22710132.
16. Furu K, Kieler H, Haglund B, Engeland A, Selmer R, Stephansson O, et al. Selective serotonin reuptake inhibitors and venlafaxine in early pregnancy and risk of birth defects: population based cohort study and sibling design. BMJ. 2015; 350:h1798. PMID: 25888213. doi: 10.1136/bmj.h1798

17. 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. PMID: 19776103. doi: 10.1136/bmj.b3569

18. Davis RL, Rubanowice D, McPhilips H, Raebel MA, Andrade SE, Smith D, et al. Risks of congenital malformations and perinatal events among infants exposed to antidepressant medications during pregnancy. Pharmacoepidemiol Drug Saf. 2007; 16(10):1086–94. doi: 10.1002/pds.1462 PMID: 17729378.

19. Ramos E, St-André M, Rey E, Oraichi D, Bérard A. Duration of antidepressant use during pregnancy and risk of major congenital malformations. Br J Psychiatry. 2008; 192(5):344–50. doi: 10.1192/bjp.bp.107.042523 PMID: 18450657.

20. Gentile S. Selective serotonin reuptake inhibitor exposure during early pregnancy and the risk of birth defects. Acta Psychiatr Scand. 2011; 123(4):266–75. doi: 10.1111/j.1600-0447.2011.01673.x PMID: 21261600.

21. Margulis AV, Abou-Ali A, Strazzieri MM, Ding Y, Kuyateh F, Frimpong EY, et al. Use of selective serotonin reuptake inhibitors in pregnancy and cardiac malformations: a propensity-score matched cohort in CPRD. Pharmacoepidemiol Drug Saf. 2013; 22(9):942–51. doi: 10.1002/pds.3462 PMID: 23733623.

22. Ban L, Gibson JE, West J, Fiaschi L, Sokal R, Smeth L, et al. Maternal depression, antidepressant prescriptions, and congenital anomaly risk in offspring: a population-based cohort study. BJOG. 2014; 121(12):1471–81. doi: 10.1111/1471-0528.12682 PMID: 24612301.

23. Louik C, Lin AE, Werler MM, Hernández-Díaz S, Mitchell AA. First-trimester use of selective serotonin-reuptake inhibitors and the risk of birth defects. N Engl J Med. 2007; 356(26):2675–83. doi: 10.1056/NEJMoa067407 PMID: 17596601.

24. Reefhuis J, Devine O, Friedman JM, Louik C, Honein MA, Study NBDP. Specific SSRIs and birth defects: bayesian analysis to interpret new data in the context of previous reports. BMJ. 2015; 351:h3190. PMID: 26156519. doi: 10.1136/bmj.h3190

25. Cole JA, Ephross SA, Cosmatos IS, Walker AM. Paroxetine in the first trimester and the prevalence of congenital malformations. Pharmacoepidemiol Drug Saf. 2007; 16(10):1075–85. doi: 10.1002/pds.1463 PMID: 17729379.

26. Myles N, Newall H, Ward H, Large M. Systematic meta-analysis of individual selective serotonin reuptake inhibitor medications and congenital malformations. Aust N Z J Psychiatry. 2013; 47(11):1002–12. doi: 10.1177/0004867413492219 PMID: 23761574.

27. Reis M, Källén B. Delivery outcome after maternal use of antidepressant drugs in pregnancy: an update using Swedish data. Psychol Med. 2010; 40(10):1723–33. doi: 10.1017/S0033291709992194 PMID: 20047705.

28. Bérard A, Zhao JP, Sheehy O. Sertraline use during pregnancy and the risk of major malformations. Am J Obstet Gynecol. 2015; 212(6):795.e1–e12. doi: 10.1016/j.ajog.2015.01.034 PMID: 25637841.

29. Nikfar S, Rahimi R, Hendoee N, Abdollahi M. Increasing the risk of spontaneous abortion and major malformations in newborns following use of serotonin reuptake inhibitors during pregnancy: A systematic review and updated meta-analysis. Daru. 2012; 20(1):75. doi: 10.1186/2008-2231-20-75 PMID: 23351929.

30. Grigoriadis S, VonderPorten EH, Mamissashvili L, Roerecke M, Rehm J, Dennis CL, et al. Antidepressant exposure during pregnancy and congenital malformations: is there an association? A systematic review and meta-analysis of the best evidence. J Clin Psychiatry. 2013; 74(4):e293–308. doi: 10.4088/JCP.1207966 PMID: 23656855.

31. Wemakor A, Casson K, Game E, Bakker M, Addor MC, Arriola L, et al. Selective serotonin reuptake inhibitor antidepressant use in first trimester pregnancy and risk of specific congenital anomalies: a European register-based study. Eur J Epidemiol. 2015. doi: 10.1007/s10654-015-0065-y PMID: 26148560.

32. Huybrechts KF, Palmsten K, Avorn J, Cohen LS, Holmes LB, Franklin JM, et al. Antidepressant use in pregnancy and the risk of cardiac defects. N Engl J Med. 2014; 370(25):2397–407. doi: 10.1056/NEJMoia1312828 PMID: 24941178.

33. Malm H, Artama M, Gissler M, Ritvanen A. Selective serotonin reuptake inhibitors and risk for major congenital anomalies. Obstet Gynecol. 2011; 118(1):111–20. doi: 10.1097/AOG.0b013e318220edcc PMID: 21646927.
34. Bérard A, Ramos E, Rey E, Blais L, St-André M, Oraichi D. First trimester exposure to paroxetine and risk of cardiac malformations in infants: the importance of dosage. Birth Defects Res B Dev Reprod Toxicol. 2007; 80(1):18–27. doi: 10.1002/brdb.20099 PMID: 17187388.

35. Alwan S, Reehu J, Rasmussen SA, Olney RS, Friedman JM, Study NBDP. Use of selective serotonin-reuptake inhibitors in pregnancy and the risk of birth defects. N Engl J Med. 2007; 356(26):2684–92. doi: 10.1056/NEJMoa066584 PMID: 17596602.

36. Colvin L, Slack-Smith L, Stanley F, Bower C. Dispensing patterns and pregnancy outcomes for women dispensed selective serotonin reuptake inhibitors in pregnancy. Birth Defects Res A Clin Mol Teratol. 2011; 91(3):142–52. doi: 10.1002/bdra.20773 PMID: 21381184.

37. EUROCAT. EUROCAT European surveillance of congenital anomalies. Guide 1.3. EUROCAT European surveillance of congenital anomalies. Guide 1.3. EUROCAT Central Registry, University of Ulster, Newtownabbey, Co Antrim, UK. Available: http://www.eurocat-network.eu/content/EUROCAT-Guide-1.3.pdf. 2005. Accessed 12 October 2016.

38. EUROCAT. EUROCAT European surveillance of congenital anomalies. Guide 1.4. EUROCAT Central Registry, University of Ulster, Newtownabbey, Co Antrim, UK. Available: http://www.eurocatnetwork.eu/content/EUROCAT-Guide-1.4-Full-Guide.pdf. 2013. Accessed 26 February 2015.

39. Greenlees R, Neville A, Addor MC, Amar E, Arriola L, Bakker M, et al. Paper 6: EUROCAT member registries: organization and activities. Birth Defects Res A Clin Mol Teratol. 2011; 91 Suppl 1:S51–S100. doi: 10.1002/bdra.20775 PMID: 21381185.

40. Charlton RA, Neville AJ, Jordan S, Pierini A, Damase-Michel C, Klungsøyr K, et al. Healthcare databases in Europe for studying medicine use and safety during pregnancy. Pharmacoepidemiol Drug Saf. 2014; 23(6):586–94. doi: 10.1002/pds.3613 PMID: 24664855.

41. EUROmediCAT. (EMC) 2015 Selective Serotonin Reuptake Inhibitor (SSRI) antidepressants in Pregnancy and Congenital Anomalies: population cohort study using linked electronic data in 3 countries V2. Deliverable number 21. Available: http://www.EUROmediCAT.eu/publicationsandpresentations/publications.

42. Kildemoes HW, Sørensen HT, Hallas J. The Danish National Prescription Registry. Scand J Public Health. 2011; 39(7 Suppl):38–41. doi: 10.1177/1403494810394717 PMID: 21775349.

43. Furu K, Wettermark B, Andersen M, Martikainen JE, Almarsdottir AB, Sørensen HT. The Nordic countries as a cohort for pharmacoepidemiological research. Basic Clin Pharmacol Toxicol. 2010; 106(2):86–94. doi: 10.1111/j.1742-7843.2009.00494.x PMID: 19961477.

44. Langhoff-Roos J, Krebs L, Klungsøyr K, Bjarnadottir RI, Källén K, Tapper AM, et al. The Nordic medical birth registries—a potential goldmine for clinical research. Acta Obstet Gynecol Scand. 2014; 93(2):132–7. doi: 10.1111/aogs.12302 PMID: 24237585.

45. Ford DV, Jones KH, Verplancke JP, Lyons RA, John G, Brown G, et al. The SAIL Databank: building a national architecture for e-health research and evaluation. BMC Health Serv Res. 2009; 9:157. doi: 10.1186/1472-6963-9-157 PMID: 19732426.

46. Lyons RA, Jones KH, John G, Brooks CJ, Verplancke JP, Ford DV, et al. The SAIL databank: linking multiple health and social care datasets. BMC Med Inform Decis Mak. 2009; 9:3. doi: 10.1186/1472-6947-9-3 PMID: 19149883.

47. Stats Wales, ELMS Welsh Government, Cardiff, Wales: Labour Force Survey, Quarterly Report issued 16th July, 2014, Reference ONS accessed on 23rd July, 2014. Available: https://statswales.gov.uk/Catalogue/Business-Economy-and-Labour-Market/People-and-Work/Labour-Market-Summary/LabourMarketSummary-by-Measure-Age-UKCountry-Quarter. Accessed 12 October 2016.

48. World Bank Group, 2014, The World Bank: Working for a world free from poverty. Browse by country, accessed 16.1.14. Available: http://www.worldbank.org/en/country#. Accessed 12 October 2016.

49. Hamer DM. Welsh Government Social Research, 2013, Cardiff, Wales—Child Poverty strategy for Wales: Baseline indicators, accessed on 1st August, 2014. Available: http://wales.gov.uk/docs/caecd/research/130314-child-poverty-strategy-wales-baseline-indicators-en.pdf. Accessed 12 October 2016.

50. Bradshaw PJ. Changing Childhood in an a changing Europe: Interdisciplinary Workshop Report, Part XIII, Fondation Europeenne de la Science. Interdisciplinary Workshop, European Science Foundation Standing Committee for the Social Sciences of the Science Fondation. Available: http://www.york.ac.uk/inst/spru/research/pdf/Changing_Childhood.pdf. Accessed 12 October 2016.

51. European Commission (2008) Objective 1: Supporting development in less prosperous regions. Accessed 4th August, 2012. Available: http://ec.europa.eu/regional_policy/archive/objective1/index_en.htm. Accessed 12 October 2016.

52. Hiemke C, Härter S. Pharmacokinetics of selective serotonin reuptake inhibitors. Pharmacol Ther. 2000; 85(1):11–28. PMID: 10674711.
53. WHO Collaborating Centre for Drug Statistics Methodology, Guidelines for ATC classification and DDD assignment 2015. Oslo, 2016. Available: http://www.whocc.no/filearchive/publications/2016_guidelines_web.pdf. Accessed 12 October 2016.

54. BNF. British National Formulary no.65. British Medical Association and the Royal Pharmaceutical Society of Great Britain, London.; 2013.

55. Van Allen M. Fetal vascular disruptions: mechanisms and some resulting birth defects. Pediatr Ann. 1981; 10(6):219–33. PMID: 7254912.

56. Wilffert B, Altena J, Tijink L, van Gelder MM, de Jong-van den Berg LT. Pharmacogenetics of drug-induced birth defects: what is known so far? Pharmacogenomics. 2011; 12(4):547–58. doi: 10.2217/ pgs.10.201 PMID: 21521026.

57. Yazdy MM, Mitchell AA, Louik C, Werler MM. Use of selective serotonin-reuptake inhibitors during pregnancy and the risk of clubfoot. Epidemiology. 2014; 25(6):859–65. doi: 10.1097/EDE. 000000000000157 PMID: 25171134

58. Werler MM, Mitchell AA, Shapiro S. First trimester maternal medication use in relation to gastroschisis. Teratology. 1992; 45(4):361–7. doi: 10.1002/tera.1420450407 PMID: 1533958

59. Burdan F, Szumilo J, Dudka J, Korobowicz A, Klepacz R. Celosomy is associated with prenatal exposure to cyclooxygenase inhibitors. Pharmacol Res. 2006; 53(3):287–92. doi: 10.1016/j.phrs.2005.12.006 PMID: 16460959

60. International Conference on Harmonisation (ICH). ICH Harmonised Tripartite Guideline for Good Clinical Practice. Institute of Clinical Research, Marlow, Buckinghamshire. 1996. Available: http://www. ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf. Accessed 2 January 2016). Number 56.

61. Morrow J, Russell A, Guthrie E, Parsons L, Robertson I, Waddell R, et al. Malformation risks of antiepileptic drugs in pregnancy: a prospective study from the UK Epilepsy and Pregnancy Register. J Neurol Neurosurg Psychiatry. 2006; 77(2):193–8. doi: 10.1136/jnnp.2005.074203 PMID: 16157661

62. Hall JG, Pauli RM, Wilson KM. Maternal and fetal sequelae of anticoagulation during pregnancy. Am J Med. 1980; 68(1):122–40. PMID: 6985765

63. Casson IF, Clarke CA, Howard CV, McKendrick O, Pennycook S, Pharao PH, et al. Outcomes of pregnancy in insulin dependent diabetic women: results of a five year population cohort study. BMJ. 1997; 315(7103):275–8. PMID: 9274545

64. Schaefer C, Peters PJ, Miller RK. Drugs during pregnancy and lactation: treatment options and risk assessment. 2nd ed. ed. Amsterdam; London: Elsevier; 2007.

65. Liu S, Joseph KS, Lisonkova S, Rouleau J, Van den Hof M, Sauer R, et al. Association between maternal chronic conditions and congenital heart defects: a population-based cohort study. Circulation. 2013; 128(6):583–9. doi: 10.1161/CIRCULATIONAHA.112.010564 PMID: 23812182

66. Jordan S, Charlton R, Tingay K, Thayer D, Davies G, Morgan M, et al. SSRI use in pregnancy: a study in 6 European databases. The International Marce Society For Perinatal Mental Health Biennial Scientific Conference, Swansea University, Swansea, Wales, UK. Abstract Booklet The Marce Society. Arch Womens Ment Health (2015) 18:269–408 P.368 10.1007 /S00737-01 4-0488-6.

67. Sweeting MJ, Sutton AJ, Lambert PC. What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. Stat Med. 2004; 23(9):1351–75. doi: 10.1002/sim.1761 PMID: 15116347

68. Simes R. An improved Bonferroni procedure for multiple tests of significance. Biometrika1986. p. 751–4.

69. Benjamini Y, Hachberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. 1995. p. 289–300.

70. StataCorp. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP. 2011.

71. Torfs CP, Christianson RE. Maternal risk factors and major associated defects in infants with Down syndrome. Epidemiology. 1999; 10(3):264–70. PMID: 10230836

72. IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.

73. NCCMH. (National Collaborating Centre for Mental Health) 2014 Antenatal and postnatal mental health: Clinical management and service guidance, updated edition, National Clinical Guideline 192. Published by The British Psychological Society and The Royal College of Psychiatrists, London. Available: https://www.nice.org.uk/guidance/cg192. Accessed 12 October 2016.

74. Hendrick V, Stowe ZN, Altshuler LL, Hwang S, Lee E, Haynes D. Placental passage of antidepressant medications. Am J Psychiatry. 2003; 160(5):993–6. doi: 10.1176/appi.160.5.993 PMID: 12727706.
75. Pop A, Lupu DI, Cherfan J, Kiss B, Loghin F. Estrogenic/antiestrogenic activity of selected selective serotonin reuptake inhibitors. Clujul Med. 2015; 88(3):381–5. doi: 10.15386/cjmed-474 PMID: 26609273.

76. Oberlander TF, Papsdorf M, Brain UM, Misri S, Ross C, Grunau RE. Prenatal effects of selective serotonin reuptake inhibitor antidepressants, serotonin transporter promoter genotype (SLC6A4), and maternal mood on child behavior at 3 years of age. Arch Pediatr Adolesc Med. 2010; 164(5):444–51. doi: 10.1001/archpediatrics.2010.51 PMID: 20439795.

77. Tracy TS, Venkataramanan R, Glover DD, Caritis SN, Units NIfCH aHDNoM-F- M. Temporal changes in drug metabolism (CYP1A2, CYP2D6 and CYP3A Activity) during pregnancy. Am J Obstet Gynecol. 2005; 192(2):633–9. doi: 10.1016/j.ajog.2004.08.030 PMID: 15696014.

78. Willner P, Scheer-Krüger J, Belzung C. The neurobiology of depression and antidepressant action. Neurosci Biobehav Rev. 2013; 37(10 Pt 1):2331–71. doi: 10.1016/j.neubiorev.2012.12.007 PMID: 23261405.

79. Wadhwa PD, Glynn L, Hobel CJ, Garite TJ, Porto M, Chicz-DeMet A, et al. Behavioral perinatology: biobehavioral processes in human fetal development. Regul Pept. 2002; 108(2–3):149–57. PMID: 12207393.

80. Sljivic S, Kamenev B, Maglajlic S, Djordjevic V, Stojanovic M, et al. Possible interactions of genetic and immuno-neuro-endocrine regulatory mechanisms in pathogenesis of congenital anomalies. Med Hypotheses. 2006; 67(1):57–64. doi: 10.1016/j.mehy.2005.07.037 PMID: 16574341.

81. Bukowski R, Hansen NI, Willinger M, Reddy UM, Parker CB, Pinar H, et al. Fetal growth and risk of stillbirth: a population-based case-control study. PLoS Med. 2014; 11(4):e1001633. doi: 10.1371/journal.pmed.1001633.

82. Carmichael SL, Ma C, Tinker S, Rasmussen SA, Shaw GM, Study NBDP. Maternal stressors and social support as risks for delivering babies with structural birth defects. Paediatr Perinat Epidemiol. 2014; 28(4):338–44. doi: 10.1111/ppe.12123 PMID: 24697924.

83. Hannerfors AK, Hellgren C, Schijven D, Iliadis SI, Comasco E, Skalkidou A, et al. Treatment with serotonin reuptake inhibitors during pregnancy is associated with elevated corticotropin-releasing hormone levels. Psychoneuroendocrinology. 2015; 58:104–13. doi: 10.1016/j.psyneuen.2015.04.009 PMID: 25978816.

84. Lattimore KA, Donn SM, Kaciroti N, Kemper AR, Neal CR, Vazquez DM. Selective serotonin reuptake inhibitor (SSRI) use during pregnancy and effects on the fetus and newborn: a meta-analysis. J Perinatal. 2005; 25(9):595–604. doi: 10.1093/jjp.211352 PMID: 16015372.

85. Stjernquist B, Kamenev B, Maglajlic S, Djordjevic V, Stojanovic M, et al. Possible interactions of genetic and immuno-neuro-endocrine regulatory mechanisms in pathogenesis of congenital anomalies. Med Hypotheses. 2006; 67(1):57–64. doi: 10.1016/j.mehy.2005.07.037 PMID: 16574341.

86. Stephansson O, Kieler H, Haglund B, Arntz M, Engelander A, Furu K, et al. Selective serotonin reuptake inhibitor antidepressants and risk of stillbirth and infant mortality. JAMA. 2013; 309(1):48–54. doi: 10.1001/jama.2012.153812 PMID: 23280224.

87. Jimenez-Solem E, Andersen JT, Petersen M, Broedbaek K, Lander AR, Alzal S, et al. SSRIs and congenital malformations following prenatal exposure to serotonin reuptake inhibitors and benzodiazepines using population-based health data. Birth Defects Res B Dev Reprod Toxicol. 2008; 83(1):68–76. doi: 10.1002/bdj.20144 PMID: 18293409.

88. Gentile S. Antipsychotic therapy during early and late pregnancy. A systematic review. Schizophr Bull. 2010; 36(3):518–44. doi: 10.1093/schbul/sbn107 PMID: 18787227.
94. Reis M, Källén B. Combined use of selective serotonin reuptake inhibitors and sedatives/hypnotics during pregnancy: risk of relatively severe congenital malformations or cardiac defects. A register study. BMJ Open. 2013; 3(2). doi: 10.1136/bmjopen-2012-002166 PMID: 23427202.

95. Coughlin CG, Blackwell KA, Bartley C, Hay M, Yonkers KA, Bloch MH. Obstetric and neonatal outcomes after antipsychotic medication exposure in pregnancy. Obstet Gynecol. 2015; 125(5):1224–35. doi: 10.1097/AOG.0000000000000759 PMID: 25932852.

96. Latendresse G, Ruiz RJ, Wong B. Psychological distress and SSRI use predict variation in inflammatory cytokines during pregnancy. Open J Obstet Gynecol. 2013; 3(1A):184–91. doi: 10.4236/ojog.2013.31A034 PMID: 24524011.

97. Eke AC, Saccone G, Berghella V. Selective serotonin reuptake inhibitor (SSRI) use during pregnancy and risk of preterm birth: a systematic review and meta-analysis. BJOG. 2016 May 30. doi: 10.1111/1471-0528.14144 PMID: 27239775.

98. Räisänen S, Lehto SM, Nielsen HS, Gissler M, Heinonen S. Risk factors for and perinatal outcomes of major depression during pregnancy: a population-based analysis during 2002–2010 in Finland. BMJ Open. 2014; 4(11):e004883. doi: 10.1136/bmjopen-2014-004883 PMID: 25398675.

99. Klemetti A, Saxén L. Prospective versus retrospective approach in the search for environmental causes of malformations. Am J Public Health Nations Health. 1967; 57(12):2071–5. PMID: 6070247.

100. Guyatt GH, Oxman AD, Sultan S, Glasziou P, Akl EA, Alonso-Coello P, et al. GRADE guidelines: 9. Rating up the quality of evidence. J Clin Epidemiol. 2011; 64(12):1311–6. doi: 10.1016/j.jclinepi.2011.06.004 PMID: 21802902.

101. Skurtveit S, Selmer R, Tverdal A, Furu K, Handal M. Drug exposure: inclusion of dispensed drugs before pregnancy may lead to underestimation of risk associations. J Clin Epidemiol. 2013; 66(9):964–72. doi: 10.1016/j.jclinepi.2013.02.011 PMID: 23800534.

102. Knudsen TM, Hansen AV, Garne E, Andersen AM. Increased risk of severe congenital heart defects in offspring exposed to selective serotonin-reuptake inhibitors in early pregnancy—an epidemiological study using validated EUROCAT data. BMC Pregnancy Childbirth. 2014; 14:333. doi: 10.1186/1471-2393-14-333 PMID: 25258023.

103. Gadkari AS, McHorney CA. Medication nonfulfillment rates and reasons: narrative systematic review. Curr Med Res Opin. 2010; 26(3):683–705. doi: 10.1185/03007990903550586 PMID: 20078320.

104. Fischer MA, Stedman MR, Lii J, Vogeli C, Shrank WH, Brookhart MA, et al. Primary medication nonadherence: analysis of 195,930 electronic prescriptions. J Gen Intern Med. 2010; 25(4):284–90. doi: 10.1007/s11606-2010-1253-9 PMID: 20131023.

105. van Geffen EC, Gardarsdottir H, van Hulten R, van Dijk L, Egberts AC, Heerdink ER. Initiation of antidepressant therapy: do patients follow the GP’s prescription? Br J Gen Pract. 2009; 59(559):81–7. doi: 10.3399/bjgp09X395067 PMID: 19192372.

106. Beardon PH, McGilchrist MM, McKendrick AD, McDevitt DG, MacDonald TM. Primary non-compliance with prescribed medication in primary care. BMJ. 1993; 307(6908):484–8. PMID: 8401129.

107. Pierpont ME, Basson CT, Benson DW, Gelb BD, Giglia TM, Goldmuntz E, et al. Genetic basis for congenital heart defects: current knowledge: a scientific statement from the American Heart Association Congenital Cardiac Defects Committee, Council on Cardiovascular Disease in the Young: endorsed by the American Academy of Pediatrics. Circulation. 2007; 115(23):3015–38. doi: 10.1161/CIRCEHA.106.183056 PMID: 17519398.

108. Jordan S, Watkins A, Storey M, Allen SJ, Brooks CJ, Garaiova I, et al. Volunteer bias in recruitment, retention, and blood sample donation in a randomised controlled trial involving mothers and their children at six months and two years: a longitudinal analysis. PLoS One. 2013; 8(7):e67912. doi: 10.1371/journal.pone.0067912 PMID: 23874465.

109. Alwan S, Chambers CD. Findings from the National Birth Defects Prevention Study: Interpretation and translation for the clinician. Birth Defects Res A Clin Mol Teratol. 2015; 103(8):721–8. doi: 10.1002/bdra.23394 PMID: 26109026.

110. Kendrick T, King F, Albertella L, Smith PW. GP treatment decisions for patients with depression: an observational study. Br J Gen Pract. 2005; 55(513):280–6. PMID: 15826435.

111. Angermeyer MC, Matschinger H, Link BG, Schomerus G. Public attitudes regarding individual and structural discrimination: two sides of the same coin? Soc Sci Med. 2014; 103:60–6. doi: 10.1016/j.soscimed.2013.11.014 PMID: 24507911.

112. Demidenko E. Sample size determination for logistic regression revisited. Stat Med. 2007; 26(18):3385–97. doi: 10.1002/sim.2771 PMID: 17149799.
114. Talbot J, Keisu M, Stahle L. Clinical Trials—Collecting Safety Data and Establishing the Adverse Drug Reaction Profile pp.215–290 (chapter 4) In: Talbot J., Aronson J. (eds) Stephens’ Detection and Evaluation of Adverse Drug Reactions: Principles and Practice. 2012; Wiley-Blackwell, Chichester (6th edition).

115. Schroll JB, Maund E, Götzsche PC. Challenges in coding adverse events in clinical trials: a systematic review. PLoS One. 2012; 7(7):e41174. doi: 10.1371/journal.pone.0041174 PMID: 22917755.

116. Rothman KJ. No adjustments are needed for multiple comparisons. Epidemiology. 1990; 1(1):43–6. PMID: 2081237.

117. Golder S, Loke YK, Bland M. Comparison of pooled risk estimates for adverse effects from different observational study designs: methodological overview. PLoS One. 2013; 8(8):e71813. doi: 10.1371/journal.pone.0071813 PMID: 23977151.

118. Bradford-Hill A. The environment and disease: association or causation. Proceedings of the Royal Society of Medicine.; 1965. p. 295–300.

119. Greenland S, Senn SJ, Rothman KJ, Carlin JB, Poole C, Goodman SN, Altman DG. Statistical tests, P values, confidence intervals, and power: a guide to misinterpretations. Eur J Epidemiol. 2016 Apr; 31(4):337–50. doi: 10.1007/s10654-016-0149-3 PMID: 27209009.

120. BNF. British National Formulary no.71. British Medical Association and the Royal Pharmaceutical Society of Great Britain, London.; 2016.

121. United Nations. The Millennium development goals report 2007. New York: United Nations, 2007.

122. Wisner K, Schaefer C. Psychotropic Drugs pp.293–339 In: Schaefer C, Peters P, Miller R. (eds) Drugs During Pregnancy and Lactation.2015; Academic Press/ Elsevier, London 3rd edition.

123. Byatt N, Deligianidis KM, Freeman MP. Antidepressant use in pregnancy: a critical review focused on risks and controversies. Acta Psychiatr Scand. 2013; 127(2):94–114. doi: 10.1111/acps.12042 PMID: 23240634.

124. Ross LE, Grigoriadis S, Mamasashvili L, Vonderporten EH, Roerecke M, Rehm J, et al. Selected pregnancy and delivery outcomes after exposure to antidepressant medication: a systematic review and meta-analysis. JAMA Psychiatry. 2013; 70(4):436–43. doi: 10.1001/jamapsychiatry.2013.684 PMID: 23446732.

125. Oberlander TF, Gingerich JA, Anzorge MS. Sustained neurobehavioral effects of exposure to SSRI antidepressants during development: molecular to clinical evidence. Clin Pharmacol Ther. 2009; 86(6):672–7. doi: 10.1038/clpt.2009.201 PMID: 19990255.

126. Palmsten K, Hernández-Díaz S, Huybrechts KF, Williams PL, Michels KB, Achtyes ED, et al. Use of antidepressants near delivery and risk of postpartum hemorrhage: cohort study of low income women in the United States. BMJ. 2013; 347:f4877. PMID: 23965506. doi: 10.1136/bmj.f4877.

127. Chambers CD, Hernandez-Diaz S, Van Marter LJ, Werler MM, Louik C, Jones KL, et al. Selective serotonin-reuptake inhibitors and risk of persistent pulmonary hypertension of the newborn. N Engl J Med. 2006; 354(6):579–87. doi: 10.1056/NEJMoa052744 PMID: 16467545.

128. Grigoriadis S, Vonderporten EH, Mamasashvili L, Tomlinson G, Dennis CL, Koren G, et al. Prenatal exposure to antidepressants and persistent pulmonary hypertension of the newborn: systematic review and meta-analysis. BMJ. 2014; 348:f6932. PMID: 24429387. doi: 10.1136/bmj.f6932.

129. Handal M, Skurtveit S, Furu K, Hernández-Díaz S, Skovlund E, Nystad W, et al. Motor development in children prenatally exposed to selective serotonin reuptake inhibitors: a large population-based pregnancy cohort study. BJOG. 2015. doi: 10.1111/1471-0528.13582 PMID: 26374234.

130. Yonkers KA, Gotman N, Smith MV, Forray A, Belanger K, Brunetto WL, et al. Does antidepressant use attenuate the risk of a major depressive episode in pregnancy? Epidemiology. 2011; 22(6):848–54. PMID: 21900825.

131. Kirsch I, Deacon BJ, Huedo-Medina TB, Scoboria A, Moore TJ, Johnson BT. Initial severity and antidepressant benefits: a meta-analysis of data submitted to the Food and Drug Administration. PLoS Med. 2008; 5(2):e45. doi: 10.1371/journal.pmed.0050045 PMID: 18303940.

132. Merchetti M, Rucci P, Bortolotti B, Bomba A, Scocco P, Kraemer HC, et al. Moderators of remission with interpersonal counselling or drug treatment in primary care patients with depression: randomised controlled trial. Br J Psychiatry. 2014; 204(2):144–50. doi: 10.1192/bjp.bp.112.122663 PMID: 24311553.

133. Yonkers KA, Wisner KL, Stewart DE, Oberlander TF, Dell DL, Stotland N, et al. The management of depression during pregnancy: a report from the American Psychiatric Association and the American College of Obstetricians and Gynecologists. Gen Hosp Psychiatry. 2009; 31(5):403–13. doi: 10.1016/j.genhosppsych.2009.04.003 PMID: 19703633.
134. NCCMH. (National Collaborating Centre for Mental Health) (2007) Antenatal and Postnatal Mental Health: The NICE Guideline on Clinical Management and Service Guidance. Published by the British Psychological Society and the Royal College of Psychiatrists, London

135. Pearlsttein T. Depression during Pregnancy. Best Pract Res Clin Obstet Gynaecol. 2015; 29(5):754–64. doi: 10.1016/j.bpo.2015.04.004 PMID: 25976080.

136. Stein A, Pearson RM, Goodman SH, Rapa E, Rahman A, McCallum M, Howard LM, Pariante CM. Effects of perinatal mental disorders on the fetus and child. Lancet. 2014 15; 384(9956):1800–19. doi: 10.1016/S0140-6736(14)61277-0. PMID: 25455250.

137. Grigoriadis S, VonderPorten EH, Mamisashvili L, Tomlinson G, Dennis CL, Koren G, Steiner M, Mousmanis P, Cheung A, Radford K, Martinovic J, Ross LE. The impact of maternal depression during pregnancy on perinatal outcomes: a systematic review and meta-analysis. J Clin Psychiatry. 2013 Apr; 74(4):e321–41. doi: 10.4088/JCP.1207968 PMID: 23656857.

138. Grote NK, Bridge JA, Gavin AR, Melville JL, Iyengar S, Katon WJ. A meta-analysis of depression during pregnancy and the risk of preterm birth, low birth weight, and intrauterine growth restriction. Arch Gen Psychiatry. 2010 Oct; 67(10):1012–24. doi: 10.1001/archgenpsychiatry.2010.1111 PMID: 20921117.

139. McDonagh M, Matthews A, Phillipi C, Romm J, Peterson K, Thakurta S, et al. Antidepressant treatment of depression during pregnancy and the postpartum period. Evidence/Technology Assessment No. 216. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 290-2007-10057-I.) AHRQ Publication No. 14-E003-EF. Agency for Healthcare Research and Quality, Rockville, MD (July 2014) Available: https://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&product id=1927. Accessed 12 October 2016.

140. Hippocrates (Translated by Jones WHS). (1923). The Hippocratic Corpus, Epidemics, book I, sect. XI. Loeb Classical Library, Cambridge, UK and London, Heineman. Available: http://archive.org/stream/hippocrates01hippuoft/hippocrates01hippuo ft_djvu.txt. Accessed Accessed 12 October 2016.

141. Hutton C, Gunn J. Do longer consultations improve the management of psychological problems in general practice? A systematic literature review. BMC Health Serv Res. 2007; 7:71. doi: 10.1186/1472-6963-7-71 PMID: 17506904.

142. Cohen LS, Altschuler LL, Harlow BL, Nonacs R, Newport DJ, Viguera AC, et al. Relapse of major depression during pregnancy in women who maintain or discontinue antidepressant treatment. JAMA. 2006; 295(5):489–507. doi: 10.1001/jama.295.5.489 PMID: 16449613.

143. Coupland C, Hill T, Morris R, Arthur A, Moore M, Hippisley-Cox J. Antidepressant use and risk of suicide and attempted suicide or self harm in people aged 20 to 64: cohort study using a primary care database. BMJ; 2015; 350:h517. PMID: 25693810. doi: 10.1136/bmj.h517.

144. Einanson A. Publishing statistically significant results with questionable clinical importance: focus on antidepressant use in pregnancy. J Clin Psychiatry. 2012; 73(11):1443–6. doi: 10.4088/JCP.12com08192 PMID: 23218161.

145. Golder S, Loke YK, Bland M. Meta-analyses of adverse effects data derived from randomised controlled trials as compared to observational studies: methodological overview. PLoS Med. 2011; 8(5): e1001026. doi: 10.1371/journal.pmed.1001026 PMID: 21559325.

146. Dietz PM, Homa D, Engeland LJ, Bunley K, Tong VT, Dube SR, Bernert JT. Estimates of nondisclosure of cigarette smoking among pregnant and nonpregnant women of reproductive age in the United States. Am J Epidemiol. 2011 Feb 1; 173(3):355–9. doi: 10.1093/aje/kwq381 PMID: 21178103.

147. Flower A, Shawe J, Stephenson J, Doyle P. Pregnancy planning, smoking behaviour during pregnancy, and neonatal outcome: UK Millennium Cohort Study. BMC Pregnancy Childbirth. 2013; 13:238. doi: 10.1186/1471-2393-13-238 PMID: 24354748.

148. Amick HR, Gartlehner G, Gaynes BN, Formes C, Asher GN, Morgan LC, et al. Comparative benefits and harms of second generation antidepressants and cognitive behavioral therapies in initial treatment of major depressive disorder: systematic review and meta-analysis. BMJ. 2015; 351:h6019. PMID: 26645251. doi: 10.1136/bmj.h6019.

149. Ionescu-Ittu R, Marelli AJ, Mackie AS, Pilote L. Prevalence of severe congenital heart disease after folic acid fortification of grain products: time trend analysis in Quebec, Canada. BMJ. 2009; 338: b1673. PMID: 19436079. doi: 10.1136/bmj.b1673.

150. Li Y, Hua Y, Fang J, Wang C, Qiao L, Wan C, et al. Performance of different scan protocols of fetal echocardiography in the diagnosis of fetal congenital heart disease: a systematic review and meta-analysis. PLoS One. 2013; 8(6):e65484. doi: 10.1371/journal.pone.0065484 PMID: 23750263.

151. American College of Obstetricians and Gynecologists’ Committee on Obstetric Practice. Committee Opinion No. 656 Summary: Guidelines for Diagnostic Imaging During Pregnancy and Lactation. Obstet Gynecol. 2016; 127(2):418. doi: 10.1097/AOG.0000000000001309 PMID: 26942384.

152. Whitworth M, Bricker L, Mullan C. Ultrasound for fetal assessment in early pregnancy. Cochrane Database Syst Rev. 2015;(7):CD007058. PMID: 26171896.