South African National Essential Medicine List
Adult Hospital Level Medication Review Process
Component: Mental Healthcare conditions

1. Executive Summary

Date: 05 March 2020
Medicine (INN): Sertraline, oral
Medicine (ATC): N06AB06
Indication (ICD10 code): (O28.8-9; P96.8-9) +(F32.0-.9; F33.0-.9; F34.1-.9; F41.0-.9; F42.0-.9)
As preferred SSRI in the treatment of depression and anxiety during pregnancy and breastfeeding for reasons of safety
Patient population: Women during pregnancy and breastfeeding or if planning a pregnancy
Prevalence of condition (South Africa): Antenatal depression 22–47%; postnatal depression 16–32%; perinatal anxiety disorders 15–23%
Level of Care: Primary level of care
Prescriber Level: Medical officer
Current standard of Care: Citalopram
Estimates of harm (NNH): Insufficient information available to estimate NNH vs other SSRIs
Primary outcome (lower risk of harm vs other SSRIs):

- *Birth defects (Gao et al. 2018;*[1] LoE II – systematic review of cohort studies):
  - Compared to other SSRIs, use of sertraline in pregnant women in the first trimester suggests the lowest risk of major congenital anomalies compared to the background rate for major congenital anomalies in pregnant women who are not exposed to sertraline, not statistically significant. The pooled RR was 1.10; 95% CI 0.99 to 1.22 (*Gao et al. 2018*[1]; LoE II – systematic review of cohort studies)
  - No distinction between sertraline and other SSRIs in cohort studies of pregnant women with psychiatric illness
  - No distinction between sertraline and other SSRIs with respect to congenital heart defects

- *Persistent pulmonary hypertension of the newborn (PPHT)* (*Masarwa et al. 2019;*[2] LoE II – systematic review of cohort studies):
  - Network meta-analysis: sertraline ranked as most likely to have lowest risk of PPHT
  - Pairwise comparison vs fluoxetine: OR 0.34 (95% CI 0.11 – 0.96)
  - Pairwise comparison vs citalopram: Not significant, OR 0.37 (95% CI 0.12 – 1.13)

- *Infant safety in breastfeeding* (*Orsolini and Bellantuono 2015;*[3] LoE II – systematic review of cohort studies and case reports)
  - Sertraline has lowest relative infant dose vs other SSRIs
  - Sertraline has fewest case reports of infant adverse effects vs other SSRIs

Motivator/reviewer name(s): Dr L. Robertson, Dr S Takuva
PTC affiliation: Gauteng Provincial PTC, Sedibeng District PTC

2. Name of author(s)/motivator(s)

Primary reviewer: Dr Lesley Robertson
Secondary reviewer(s): Dr Simba Takuva

3. Author affiliation and conflict of interest details

- Dr Lesley Robertson: Affiliated to the University of the Witwatersrand, the South African Society of Psychiatrists, Adult Hospital Level Committee member (2017-2020). Conflict of interests: Dr Reddys: Annual congress attendance and accommodation, 2014 – 2019; AstraZeneca: Lunch 25 July 2017; Sanofi: Lunch 21 March 2018; Lundbeck: Lunch 29 January 2019.
  Note: Dr Lesley Robertson recused from the final decision-making process regarding a recommendation.
- Dr Simba Takuva: Perinatal HIV Research Unit, Faculty of Health Sciences, University of the Witwatersrand and School of Health Systems and Public Health, Faculty of Health Sciences, University of Pretoria; no interests to declare in respect of sertraline.

4. Introduction/Background

A request was made by Prof. S. Honikman, founder and director of the Perinatal Mental Health Project, Alan J. Flisher Centre for Public Mental Health, Department of Psychiatry and Mental Health, UCT, and co-opted onto the Adult Hospital Expert Review Committee for maternal mental health, to have sertraline on the NEML as the preferred medication for perinatal treatment of depression and anxiety disorders

Rationale for sertraline as preferred antidepressant in pregnancy

- Untreated perinatal depression and anxiety negatively affects maternal engagement with healthcare services, self-care, partner relationships, and attentiveness to the infant or child.[4,5] The NDOH Adult Hospital Standard Treatment Guidelines, 2019 edition, recommend treatment of perinatal depression and anxiety.
- Sertraline is effective in the treatment of depression and anxiety.[6] In acute treatment of depression, sertraline has a higher ranking in efficacy than either fluoxetine or citalopram. In acute treatment of anxiety, sertraline and fluoxetine, but not citalopram, have evidence of efficacy (this may be related to an absence of evidence for citalopram).
- The NICE cg 192[5] for antenatal and postnatal mental health found no increased risk of any congenital malformations or cardiac malformations for sertraline.
- Sertraline may be preferred in breastfeeding as low to non-detectable serum levels have been found in exposed infants.[7] Although the metabolite of sertraline, N-desmethylsertraline, is transferred into breastmilk and has a longer half-life than sertraline, it has very low activity levels and is of unclear clinical importance.
- Sertraline may prevent postpartum depression (one very small study of sertraline (n=14) vs placebo (n=8), whereby one person in the sertraline arm developed depression vs four in the placebo arm).[8] There is an absence of evidence for the other SSRIs.
- There is agreement among international clinical guidelines to use sertraline in the treatment of new episodes of perinatal depression or anxiety, mainly related to its apparent safety in breastfeeding.[9] There are however differences in whether or not to switch antidepressants in pregnant women already on treatment.

Prevalence of perinatal depression and anxiety

For high-income countries, Howard et al (2014)[10] cite prevalence rates of 3.1–4.9% for perinatal major depression and of 13% for anxiety disorders. For LMICs, Gelaye et al (2016)[11] found pooled prevalence rates from over 50 studies of 25.8% for antenatal depression and 19.6% for postpartum depression. Fekadu et al (2020)[12] found antenatal depression to be more common in low-income countries (34%) than in middle-income countries (23%). In South Africa, prevalence rates of antenatal depression vary between 22% in Cape Town and 47% in rural KZN, [3-6] and rates of 45%[17] and 55%[16] have been found among HIV infected women. For postnatal depression, prevalence rates of 16%[18] and 24%[19] have been found in Soweto, 32%[20] in Cape Town, and 35%[17] among HIV infected women in Mpumulanga. Anxiety disorders were found to occur in 23% of a sample of pregnant women in Hanover Park, Cape Town,[21] and in 15% of a sample in Soweto.[14]

Maternal and child outcomes associated with untreated perinatal depression and anxiety

Globally, untreated antenatal depression is associated with 1.6 times increased risk of preterm delivery and double the risk of low birth weight babies compared to women without depression.[22] For LMICs, Fekadu et al (2020)[12] found antenatal depression to be associated with 2.4 times the risk of preterm birth and 1.7 times for low birth weight. In LMICs, postnatal depression is associated with cessation of breastfeeding, higher rates of diarrhoea and febrile illnesses among infants, poor infant cognitive, motor, and social development, and stunted growth in early childhood.[11] As with antenatal depression, antenatal anxiety is associated with an increased risk of preterm birth and low birth weight as well as small for gestational age infants.[23] Maternal anxiety disorders are also associated with a range of childhood neurodevelopmental and psychiatric disorders.[4] In general, poor pregnancy outcomes tend to increase with increased severity of depression or anxiety.

Evaluation of risks associated with antidepressants in pregnancy

While shared genetic risk is likely to contribute to increased neurodevelopmental and psychological problems in offspring, the risk factors for perinatal depression and anxiety (including maternal childhood abuse, intimate partner violence, low socio-economic status, food insecurity) all increase the risk of poor pregnancy outcomes.[4,5] In addition, women with depression and anxiety are more likely to use tobacco, alcohol, and other substance use than those without a mental illness. Thus, there are multiple confounding factors in assessing the risk of antidepressant treatment in pregnancy, including confounding by indication.

Two systematic reviews which attempted to address confounding by indication (Mitchell and Goodman, 2018;[24] Prady et al., 2018[25]) found that the risk of low birth weight babies did not differ between treated and untreated depression. Mitchell and Goodman also found that while gestational age was slightly shorter (approximately 3-10 days) among treated vs untreated

depression, a relationship between treatment and preterm delivery was unclear. Examining neurodevelopmental and neurobehavioural outcomes, Prady et al. found no detrimental effects associated with antidepressant treatment in pregnancy. These authors conclude that the evidence does not support discontinuation or withholding of antidepressants in pregnancy with regards to gestational age, birth weight, or neurodevelopmental outcomes.

Other maternal outcomes associated with antidepressant treatment include gestational hypertension and pre-eclampsia (Guan et al., 2018[26]) and postpartum haemorrhage (Jiang et al., 2016[27]). However, some uncertainty exists regarding these risks related to high heterogeneity between studies and difficulty in adjusting for all confounding variables. While, Jiang et al (2016) suggest that antidepressants are associated with an increased risk of postpartum haemorrhage, they do not distinguish between SSRIs.

Although the impact of antenatal treatment of depression and anxiety on maternal and fetal outcomes of pregnancy is not known, it may improve childhood behavioural outcomes. With uncertainty regarding risks of antidepressants in pregnancy, and the possibility of benefit in relieving symptoms and improving uptake of healthcare services, the NICE guideline for antenatal and postnatal mental health (NICE cg 192, 2014)[5] recommends that the "threshold for the prescribing of antidepressants should be adjusted in comparison to that for nonpregnant women and that there should be an increased level of monitoring and support for women taking antidepressants in pregnancy and the postnatal period."

However, NICE does not recommend any antidepressant over another. Results of their evidence synthesis of studies published in any language up until April 2014 are summarised in Table 1. Note that these are from cohort studies of the general female population, without matched controls, and therefore no adjustment for confounding variables, including confounding by indication. The NNH is calculated directly from the number of events as provided by NICE.

Table 1. Risks associated with antenatal use of antidepressants according to NICE clinical guideline 192[5]

Condition	Medicine	Random effects, OR (95% CI)	NNH
Congenital malformations	Paroxetine	1.20 (1.00, 1.43)	225
Major congenital malformations	Paroxetine	1.34 (1.01, 1.78)	127
	Fluoxetine	1.27 (1.06, 1.51)	126
Cardiac malformations	Paroxetine	1.46 (1.12, 1.90)	323
	Fluoxetine	1.58 (1.08, 2.32)	221
ASD	No SSRIs associated with a significant effect (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline included)		
VSD	Citalopram	1.49 (1.07, 2.07)	240
	Fluoxetine	1.65 (1.12, 2.44)	178
	Escitalopram,	2.11 (1.05, 4.24)	106
Miscarriage	SSRIs	1.60 (1.01, 2.53)	36
Preterm delivery	SSRIs	Not significant, 1.38 (0.99, 1.92)	20
Poor neonatal adaptation syndrome	Any antidepressant	4.13 (2.14, 7.98)	4
Persistent pulmonary hypertension of the newborn	SSRIs	2.51 (1.78, 3.54)	558
Neonatal respiratory distress	Any antidepressant	1.89 (1.68, 2.13)	11
Neonatal tremors	Any antidepressant	8.14 (4.23, 15.65)	3

5. Purpose/Objective

To ascertain if sertraline should be recommended as a preferred SSRI during pregnancy and breastfeeding

- P: Women in the perinatal period

- **I**: Sertraline
- **C**: Other SSRIs
- **O**: Maternal and fetal outcomes of pregnancy (congenital malformations, miscarriage, persistent pulmonary hypertension of the newborn (PPHT), postnatal adaptation syndrome/neonatal distress or tremors, gestational hypertension or pre-eclampsia, post-partum haemorrhage); infant safety in breastfeeding.

6. Methods

Search strategy

- To obtain evidence published since the NICE cg192, PubMed was searched on 17th February 2020 for systematic reviews and meta-analyses published in English between 01/01/2014 and 31/12/2020. MeSH Terms: sertraline; serotonin uptake inhibitors; antidepressive agents; pregnancy; breast feeding. The Cochrane database of systematic reviews was searched on 26/02/2020 using terms antidepressants OR SSRIs OR sertraline in All Text AND perinatal OR pregnancy OR breastfeeding in Title Abstract Keyword with no date restrictions.

- Only systematic reviews with or without meta-analysis which distinguished between the different SSRIs for maternal, fetal, infant or child outcomes of pregnancy and breastfeeding were included in the evidence synthesis.

Results

- Of 95 titles retrieved (79 from PubMed; 20 from Cochrane Library; 4 duplicates), three were selected for decision-making and are described in Table 2.
- Search results and reasons for study exclusion from the evidence synthesis are attached in appendix I (PubMed) and appendix II (Cochrane).

Table 2. Systematic reviews included in evidence synthesis and decision making

Paper	AMSTAR 2	Notes	Funding Source
Masarwa et al. 2019[2] Prenatal exposure to selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors and risk for persistent pulmonary hypertension of the newborn: a systematic review, meta-analysis, and network meta-analysis	13/ 16 items fulfilled Item 5: not stated if study selection in duplicate Item 7: no list of excluded studies Item 10: no reporting of funding sources for included studies	11 studies included - 8 cohort studies - 3 case-control studies N=7 080 850 infants (156 978 exposed to an SSRI) Population of pregnant women: Details not provided for cohort or case-control studies Adjusted effects used where available (random effects model used in meta-analysis). - 3 studies did not report any covariate adjustment - 3 studies excluded newborns with cardiac or pulmonary disease or meconium aspiration; 1 study analysed these separately	No external funding
Gao et al. 2018[1] Selective serotonin reuptake inhibitor use during early pregnancy and congenital malformations: a systematic review and meta-analysis of cohort studies of more than 9 million births	14/ 16 items fulfilled Item 7: no list of excluded studies Item 10: no reporting of funding sources for included studies	29 cohort studies included N=9 085 954 infants (59 894 exposed to an SSRI) Population of pregnant women with 1st trimester SSRI use: 25 studies: general population 8 studies: women with psychiatric illness (4 studies included both) Adjusted effects used where available (random effects model used in meta-analysis). - 9 studies did not report any covariate adjustment - 15 studies did not control for maternal smoking/alcohol use - 11 studies did not control for maternal age	National Key R&D Program of China (no.2017YFC0907400 to Y-HZ); the Science and Technology Project of Liaoning Province (no. 2013225079 to Y-HZ); the Natural Science Foundation of China (no. 81602918 to Qi-Jun Wu), the Doctoral Start-up Foundation of Liaoning Province (no. 201501007 to Qi-Jun Wu), the Younger research fund of Shengjing Hospital (grant 2014sj09 to Qi-Jun Wu), and the Outstanding Youth Foundation of China Medical University (no. YQ20170002 to Qi-Jun Wu).
Orsolini and Bellantuono 2015[3] Serotonin reuptake inhibitors and breastfeeding: a systematic review	4/ 12 items fulfilled Items 11, 12, 14, 15: not applicable (no meta-analysis) Item 2: no à priori protocol Item 6: data extraction not in duplicate Item 7: no list of excluded studies Item 8: included studies only partially described – no detail re covariates or follow-up period	Systematic review on neonatal safety profile of SSRIs and breastfeeding – included case reports, prospective or retrospective cohort studies and clinical trials: Citalopram (CIT): 7 case reports and 7 prospective studies, N=112 cases exposed Escitalopram (ESC): 5 case reports and 3 prospective studies, N=37 Fluoxetine (FLX): 5 case reports, 14 prospective studies, 1 retrospective study, and 1 open trial, N=280	Not stated, although authors declared no conflict of interest

	Items 9and 13: no risk of bias assessment Item 10: no reporting of funding sources for included studies Item 16: funding for the review not stated	Fluvoxamine (FLV): 7 case reports and 4 prospective studies, N=18 Paroxetine (PAR): 3 case reports and 14 prospective studies, N=228 Sertraline (SER): 6 case reports, 13 prospective studies, 2 pilot studies and 1 random controlled trial, N=279	

Evidence synthesis

Maternal outcomes

- No studies were identified which differentiated between SSRIs for gestational hypertension, pre-eclampsia, or postpartum haemorrhage

Congenital Malformations – *Gao et al. 2018*[1] (events of included studies not provided, NNH not available)

- Major Congenital Anomalies
  - Vs general population: sertraline showed the lowest risk of major congenital anomalies (not statistically significant)
  - Vs women with psychiatric illness: no distinction between SSRIs – all showed no significantly increased risk

Table 3. Major Congenital Anomalies (Gao et al. 2018)

Medicine	Cohort design			Restricted to women with psych illness		
	Studies	OR (95% CI)	I^2	Studies	OR (95% CI)	I^2
SSRIs	9 Studies	**1.11 (1.03, 1.19)**	38.4%	4 Studies	1.04 (0.95, 1.13)	2.5%
Citalopram	8 studies	**1.19 (1.09, 1.31)**	13.4%	2 studies	1.17 (0.84, 1.62)	66.0%
Fluoxetine	11 studies	**1.17 (1.07, 1.28)**	0.0%	2 studies	0.84 (0.67, 1.05)	0.0%
Paroxetine	11 studies	**1.18 (1.05, 1.32)**	0.0%	2 studies	1.17 (0.97, 1.41)	0.0%
Sertraline	9 studies	1.10 (0.99, 1.22)	0.0%	2 studies	1.12 (0.87, 1.44)	0.0%

- Congenital Heart Defects
  - Vs general population: no distinction between SSRIs – all showed increased risk
  - Vs women with psychiatric illness: no distinction between SSRIs – all showed no significantly increased risk

Table 4. Congenital Heart Defects (Gao et al. 2018)

Medicine	Cohort design			Restricted to women with psych illness		
	Studies	OR (95% CI)	I^2	Studies	OR (95% CI)	I^2
SSRIs	18 Studies	**1.24 (1.11, 1.37)**	59.0%	6 Studies	1.06 (0.90, 1.26)	33.9%
Citalopram	11 studies	**1.24 (1.02, 1.51)**	52.5%	2 studies	1.08 (0.75, 1.56)	0.0%
Fluoxetine	14 studies)	**1.30 (1.11, 1.53)**	29.3%	3 studies	0.94 (0.65, 1.37)	41.9%
Paroxetine	16 studies	**1.35 (1.19, 1.53)**	0.0%	3 studies	1.27 (0.89, 1.80)	72.3%
Sertraline	13 studies	**1.42 (1.12, 1.80)**	63.9%	3 studies	1.12 (0.92, 1.35)	0.0%

- Specific congenital heart defects
  - All associations derived from general population cohort studies and therefore may be related to confounding factors. Sertraline exposure in pregnancy associated with increased risk of ASD but not RVOTD (compared to general population).

Table 5. Specific congenital heart defects (Gao et al. 2018)

CHD	Medicine	Relative Risk (95% CI)
Septal defects	SSRIs	**1.38 (1.00, 1.91)**
	Citalopram	**1.81 (1.22, 2.68)**
	Fluoxetine	**1.65 (1.02, 2.67)**
	Sertraline	**2.69 (1.76, 4.10)**
ASD	SSRIs	**1.83 (1.22, 2.73)**

	Sertraline	**2.07 (1.26, 3.39)**
RVOTD	SSRIs	**1.38 (1.09, 1.75)**
	Citalopram	**1.59 (1.08, 2.35)**
	Fluoxetine	**1.63 (1.11, 2.41)**
	Paroxetine	**2.15 (1.04, 4.44)**

ASD=Atrial septal defect; RVOTD=right ventricular outflow tract defects

- Other system-specific malformations
  - All associations derived from general population cohort studies and therefore may be related to confounding factors. Sertraline exposure in pregnancy associated with increased risk of respiratory system and limb defects and clubfoot compared to general population.

Table 6. Other system-specific malformations (Gao et al. 2018)

Malformation	Medicine	Relative Risk (95% CI)
Neural Tube Defects	SSRIs	**1.49 (1.05, 2.10)**
	Fluoxetine	**2.28 (1.28, 4.06)**
Eye defects	Citalopram	**2.00 (1.13, 3.54)**
	Paroxetine	**2.26 (1.26, 4.04)**
Ear, face, neck defects	Fluoxetine	**3.45 (1.28, 9.29)**
Cleft palate	Paroxetine	**2.82 (1.26, 6.32)**
Respiratory system defects	Sertraline	**2.65 (1.32, 5.32)**
Abdominal wall defects	SSRIs	**1.81 (1.22, 2.68)**
Omphalocele	SSRIs	**1.73 (1.03, 2.89)**
Gastroschisis	SSRIs	**1.89 (1.19, 3.00**
Limb defects	Sertraline	**1.42 (1.03, 1.95)**
Clubfoot	SSRIs	**1.30 (1.06, 1.61)**
	Sertraline	**1.72 (1.11, 2.65)**
Cystic kidney disease	SSRIs	**2.96 (1.87, 4.70)**
Urinary system defects	Citalopram	**1.87 (1.23, 2.83)**
Hypospadias	Citalopram	**1.87 (1.23, 2.83)**

Persistent Pulmonary Hypertension of the Newborn (PPHT) – *Masarwa et al. 2019*[2]

- Meta-analysis of 11 studies suggests an increased risk of PPHT with SSRI exposure, NNH 1000
  - Sensitivity analyses confirm the increased risk (Table 7).
  - Note that the three case-control studies yielded very different NNH:
    - Chambers et al. (2006), n=1213, NNH 3
    - Källen and Olausson (2008), n=831 324, NNH 677
    - Wilson et al. (2011), n=140, NNH -7 (no events in exposed neonates)

Table 7. Association of PPHT with antenatal SSRI exposure

Analysis	Studies		Random effects OR (95% CI)	I^2	NNH
All studies: cohort design	8	n=6 248 173	**1.58 (1.14, 2.19)**	72%	1195
All studies: case-control	3	n=832 677	**3.63 (1.64, 8.04)**	26%	149
All studies: total	11	n=7 080 850	**1.82 (1.31, 2.54)**	72%	977
Only studies reporting adjusted effects	8	n=6 873 165	**aOR 2.42 (1.68, 3.48)**	69%	896
Only high quality studies	7	n=6 048 638	**1.99 (1.43, 2.78)**	75%	749
Exposure after week 20: cohort design	6	n=5 959 231	**1.94 (1.35, 2.79)**	78%	744
Exposure after week 20: case-control	2	n=1 353	**2.21 (0.20, 24.13)**	62%	4
Exposure after week 20: total	8	n=5 960 584	**2.08 (1.44, 3.01)**	76%	720

- Network meta-analysis: pairwise comparison (Figure 1):

- Sertraline ranked as most likely to have lowest risk for PPHT
- Vs fluoxetine: OR 0.34 (95% CI 0.11 – 0.96)
- Vs other SSRIs: non-significant

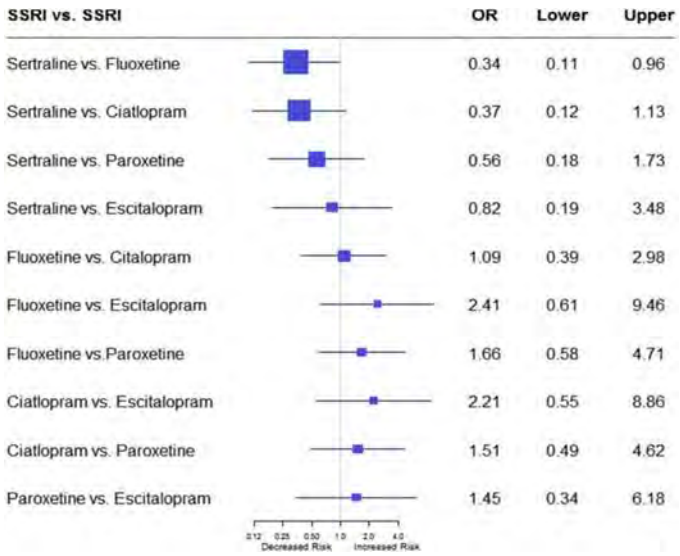

Fig 1. Pairwise network meta-analysis for different SSRIs

- Network meta-analysis: probability (*P*) score
  - Sertraline has highest *P* score (0.83), meaning lowest probability of PPHT

Table 8. *P* score for PPHT

Medication	*P* score
Sertraline	.83
Escitalopram	.69
Paroxetine	.49
Citalopram	.21
Fluoxetine	.16

Other obstetric or neonatal outcomes

- No studies were identified which differentiated between SSRIs for preterm labour, low birth weight, poor neonatal adaptation syndrome, or neonatal distress.

Breastfeeding – *Orsolini and Bellantuono 2015*

The relative infant dose, milk and plasma concentrations, and reported neonatal adverse effects are summarised in Table 9 for citalopram, fluoxetine, paroxetine, and sertraline. Fluvoxamine and escitalopram have been omitted from the table as sample sizes were too small (n=18 and 37 respectively) to draw any conclusions.

- Sertraline has lowest relative infant plasma dose (0.54–2.2%)
- Sertraline has lowest infant plasma detection rate of the medicine (detected in 9.7% of cases (n=134)). Detection rate of metabolite (23.7% of cases, n=114) lower than fluoxetine but not citalopram. However, the metabolite of citalopram was measured in a very low number of cases (n=21).
- Sertraline has lowest number of reported neonatal adverse events (n=1, vs 2 for paroxetine, 6 for citalopram, and 11 for fluoxetine).

Table 9. SSRI exposure during breastfeeding (Orsolini and Bellantuono, 2015)

	Citalopram N=112 Daily dose range 10 – 80mg	**Fluoxetine** N=280 Daily dose range 10 – 80mg	**Paroxetine** N=228 daily dose range 5 to 60mg.	**Sertraline** N=279 daily dose range 25 to 300 mg.
Relative infant dose	0.2 to 5.9% 8 studies (n=37)	0.54% to 6.81% 7 studies (n=66)	0.34% to 3% 7 reports (n=58)	0.54% to 2.2% 5 reports (n=51)
Milk concentration - medicine	41–1190 ng/mL 8 studies (n=27)	3–578 ng/mL 14 studies (n=109)	2–776 ng/mL 9 studies (n=91)	8.4–4640 ng/mL 6 studies (n=75)
Milk concentration - metabolite	25–150ng/mL 3 studies (n=10)	2–314 ng/mL 11 studies (n=103)	NA	15–7897 ng/mL 5 studies (n=69)
Infant plasma concentration - medicine	1.4–98.9 ng/mL 7 studies (n=33) Detected in 45.5% of cases (n=15)	1–304 ng/mL 14 studies (n=105) Detected in 39% of cases (n=41)	0.95–188 ng/mL 10 studies (n=87) detected in 35.6% of cases (n=31)	2–87 ng/mL 14 studies (n=134) Detected in 9.7% of cases (n=13)
Infant plasma concentration - metabolite	1.4ng/mL 4 studies (n=21) Detected in 9.5% of cases (n=2)	1.4–640ng/mL 13 studies (n=101), Detected in 81% of cases (n=82)	NA	1.6–145 ng/mL 9 studies (n=114) Detected in 23.7% of cases (n=27)
Milk: Plasma ratio - medicine	0.93 to 4.3 10 studies (n=40)	0.01 to 6.09 11 studies (n=96)	0.056 to 1.3 9 studies (n=91)	0.42 to 4.81 8 studies (n=84)
Milk: Plasma ratio - metabolite	0.9 to 6.3 5 studies (n=32)	0.08 to 2.08 9 studies (n=94)	NA	0.42 to 4.81 4 studies (n=50)
Reported neonatal adverse events	6 (n=112)	11 (n=280)	2 (n=228)	1 (n=279)
	Transient neurodevelopmental delay spontaneously resolved	5 cases of decreased postnatal growth	Lethargy, poor weight gain and hypotonia	Benign neonatal sleep myoclonus
	2 cases of colic and decreased feeding	2 cases of colic	Irritability	-
	Irritability/ restlessness	Irritability and restlessness	-	-
	Uneasy sleep	Watery stools, uncontrollable crying, vomiting and decreased sleep	-	-
	Irregular breathing, sleep disorders and hypo/hypertonia. This resolves spontaneously.	Possible seizure, unresponsive and cyanotic	-	-
	-	Somnolence, lethargy, fever and unresponsiveness	-	-

7. Alternative agents

- Citalopram (current standard of care during pregnancy): risk of major birth defects not significant when analysis restricted to women with psychiatric illness; ranks more likely than sertraline in risk of PPHT of the newborn but not significant on pairwise comparison. Clinical importance of the higher relative infant dose in breastfeeding is unclear; neonatal adverse events in 5% of cases, with no evaluation of confounding factors.
- Fluoxetine, on the NEML, but avoidance of use in pregnancy is recommended because of long half-life and high transfer across placenta and into breastmilk. However, risk of major birth defects not significant when analysis restricted to women with psychiatric illness; ranks as highest probability of PPHT of the newborn and significantly more likely than sertraline on pairwise comparison. Clinical importance of the higher relative infant dose in breastfeeding is unclear; neonatal adverse events in 4% of cases, with no evaluation of confounding factors
- Paroxetine, not on the NEML. Appears to be the most suitable alternative during breastfeeding. However, citalopram is the preferred alternative during pregnancy in several international clinical guidelines,[9] related to an increased risk of 1st trimester

exposure to paroxetine with major congenital anomalies and congenital heart defects. While this evidence synthesis did not find a greater association of birth defects with paroxetine than with other SSRIs, it also did not specifically evaluate for such an association, and it is not clear if such a caution is warranted as no increased risk when analysis restricted to women with psychiatric illness.

8. Interpretation of the evidence and comments

There is a need to treat depression and anxiety during pregnancy and breastfeeding. SSRIs are first line treatment for depression, anxiety, and post-traumatic stress disorder. While SSRIs are associated with possible harms to the mother and/or baby, there is high heterogeneity among studies and in degree of adjustment for covariates and confounding by indication.

Nevertheless, the evidence suggests that sertraline may be safer than:

- fluoxetine or citalopram in pregnancy with respect to major congenital anomalies in observational studies of women in the general population. However, in studies restricted to women with psychiatric illness, there is a suggestion of no evidence of harm from any of the SSRIs.
- fluoxetine on pairwise comparison, and other SSRIs in probability ranking, with respect to persistent pulmonary hypertension of the newborn; and
- fluoxetine or citalopram in breastfeeding.

This safety profile is consistent with sertraline having a low rate of placental transfer, is highly protein bound, a short half-life, and metabolism by several different P450 enzymes.[2,3,28]
However, the evidence is weak and the clinical impact is unclear.

EVIDENCE TO DECISION FRAMEWORK

	JUDGEMENT	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE	**What is the overall confidence in the evidence of effectiveness?** Confident [X] Not confident [ ] Uncertain [ ]	Network meta-analysis of RCTs by Cipriani et al, 2018 (refer to the South African National Essential Medicines List Primay and Adult Hospital Level Medication Review. SSRIs for depression and anxiety, July 2018).[6]
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Benefits outweigh harms [X] Harms outweigh benefits [ ] Benefits = harms or Uncertain [ ]	Evidence from an underpowered sub-analysis of an observational study suggests that SSRIs, as a class, are associated with a non-significant risk of major congenital anomalies compared to the background rate for major congenital anomalies in pregnant women with psychiatric illnesses, who are not exposed to SSRIs.[1] Sertraline ranked as most likely to have lowest risk for PPHT.[2]
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: n/a Yes [ ] No [X] List the members of the group: n/a	Sertraline is preferred to citalopram due to the apparent better safety profile in breastfeeding (lower infant serum concentrations and fewer neonatal ADRs) and a lower probability of causing PPHTN. Citalopram may be considered when sertraline is unavailable; though there is insufficient evidence for escitalopram regarding safety in breastfeeding and thus is not recommended for maternal mental health.

VALUES & PREFERENCES / ACCEPTABILITY

Is there important uncertainty or variability about how much people value the options?

Minor	Major	Uncertain
X		

Is the option acceptable to key stakeholders?

Yes	No	Uncertain
		X

RESOURCE USE

How large are the resource requirements?

More intensive	Less intensive	Uncertain
X		

Medicine	Cost (ZAR)
Sertraline 100 mg, 30 tablets	35.84 to 53.76*
Citalopram 20 mg, 30 tablets	11.54**

*SEP database, accessed 21 May 2020: 40 to 60% of SEP (Prices for the 5 cheapest generic products were used - Aurolift®, Dyna-sertraline®, Serdep 100®, Serlife 100®, Zolid 100®).
https://mpr.code4sa.org/
** Contract circular RT289-2019 (Accessed 21 May 2020) - weighted average price calculated.

Epidemiology:

Assumptions:

- Social intervention initiated prior to pharmacotherapy.
- Response is assumed to be determined after a minimum of 4 months of pharmacotherapy.
- General treatment course for a patient responding to pharmacotherapy is assumed to be a minimum of 12 months.
- Majority of pregnant women would respond to SSRI therapy; but estimate that approximately 60% would respond to SSRI therapy (Cipriani et al, 2018; Expert opinion).
- Target coverage of mental health illness estimated to be approximately 30% (Lund et al, 2009).
- Patients are stabilised on maintenance dose; and thus sertraline 100 mg daily and citalopram 20 mg daily.
- Prevalence of antenatal depression: 22–47%.
- Prevalence of postnatal depression: 16–32%
- Prevalence of perinatal anxiety disorders: 15–23%

Using birth statistics from StatsSA midyear population statistics for 2019, the estimated annual budget for treating maternal mental health (for the indications of antenatal and postnatal depression and perinatal anxiety disorders) was calculated to be:

A: Sertraline (lower limit; upper limit)
R119 461 136 (R54 464 002; R262 043 783)

B: Citalopram (lower limit; upper limit)
R25 646 007 (R17 538 560; R33 753 455)

C: Incremental budget impact if the safer agent, sertraline was used:
R93 815 129 (R36 925 442; R228 290 328)

Limitations of this model:

		• There isn't a contract/tender price for sertraline 100 mg tablets currently – estimates were based on the average of a proportion of current SEP. • Real-time data for the uptake of maternal mental health care is lacking and was based on historic projected NDoH targets from 2002. • Adverse effects associated with citalopram were not costed into this costing analysis. **References:** [1] StatsSA. Mid-year population estimates, 2019. http://www.statssa.gov.za/ [2] South African National Essential Medicines List Primay and Adult Hospital Level Medication Review. SSRIs for depression and anxiety [Internet]. 2018. Available from: http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/404-phc-medicines-reviews 3] Dewing S, Tomlinson M, Le Roux IM, Chopra M, Tsai AC. Food insecurity and its association with co-occurring postnatal depression, hazardous drinking, and suicidality among women in peri-urban South Africa. J Affect Disord [Internet]. 2013;150(2):460–5. Available from: http://dx.doi.org/10.1016/j.jad.2013.04.040 [4] Verkuijl NE, Richter L, Norris SA, Stein A, Avan B, Ramchandani PG. Postnatal depressive symptoms and child psychological development at 10 years: A prospective study of longitudinal data from the South African Birth to Twenty cohort. The Lancet Psychiatry [Internet]. 2014;1(6):454–60. Available from: http://dx.doi.org/10.1016/S2215-0366(14)70361-X [5] Redinger S, Norris SA, Pearson RM, Richter L, Rochat T. First trimester antenatal depression and anxiety: Prevalence and associated factors in an urban population in Soweto, South Africa. J Dev Orig Health Dis. 2018;9(1):30–40. https://pubmed.ncbi.nlm.nih.gov/28877770/ [6] Heyningen T Van, Honikman S, Myer L, Onah MN, Tomlinson M, Project MH, et al. Prevalence and predictors of anxiety disorders amongst low- income pregnant women in urban South Africa: a cross sectional study. Arch Womens Ment Health. 2018;20(6):765–75. [7] Lund et al, 2009 [8] Cipriani A, Furukawa TA, Salanti G, Chaimani A, Atkinson LZ, Ogawa Y, et al. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. Lancet. 2018;391(10128):1357-66.
EQUITY	**Would there be an impact on health inequity?** Yes ☐ No ☒ X Uncertain ☐	
FEASIBILITY	**Is the implementation of this recommendation feasible?** Yes ☐ No ☒ X Uncertain ☐	Dependant on availability and access of sertraline with price being a major factor.

Type of recommendation	We recommend against the option and for the alternative	We suggest not to use the option or to use the alternative	We suggest using either the option or the alternative	We suggest using the option	We recommend the option
	☒ X	☐	☐	☐	☐

Recommendation

Based on the evidence review, the Adult Hospital Level Committee does not recommend sertraline for perinatal psychiatric conditions. Evidence from an underpowered sub-analysis of an observational study suggests that SSRIs, as a class, are associated with a non-significant risk of major congenital anomalies amongst pregnant women with psychiatric illnesses. In clinical practice, sertraline is the preferred agent. However, until there is price parity between sertraline and citalopram, the current standard of care will be retained as citalopram in this clinical setting.

The advantage of sertraline over citalopram (reduction in persistent pulmonary hypertension of the newborn and decreased transmission through breastfeeding) does not justify the additional cost.

Level of Evidence: II Meta-analyses and systematic reviews of RCTs of low to moderate quality [1]

Review indicator: *Price reduction comaparable to citalopram*

Evidence of efficacy	Evidence of harm	Price reduction
		X

VEN status: n/a

Vital	Essential	Necessary

NEMLC MEETING OF 11 JUNE 2020:

NEMLC noted that SSRIs are associated with a non-significant risk of major congenital anomalies amongst pregnant women with psychiatric illnesses. This was based on an underpowered sub-analysis of an observational study. In clinical practice, sertraline is the preferred agent. However, until there is price parity between sertraline and citalopram, the current standard of care will be retained as citalopram in this clinical setting.

Monitoring and evaluation considerations: Monitoring of price; and once price reduced sufficiently for inclusion on the National EML – use for other indications requires monitoring (e.g.: schizophrenia).

Research priorities: n/a

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