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# Escitalopram Induced Congenital, Familial and Genetic Disorders and its Safety in Pregnancy: a Review of Post Marketing Safety Data

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## ABSTRACT

**Background:** The aim of this paper is to report escitalopram induced congenital, familial and genetic disorders and its safety in pregnancy, a review of post marketing safety data. The primary focus of the safety monitoring practice iscollection, assessment and reporting of the adverse events(AEs) to medicinal products approved for differentMarketing Authorisation Holders (MAHs).

**Materials and Methods**: Cumulative data of Individual Case Safety Reports (ICSRs) received from different sourceswithin the time frame of 2014 to 2018 were studied. The ADRs reported to the SOCs (System Organ Class), (a) congenital, familial and genetic disorders and (b) Pregnancy, puerperium and perinatal conditions were focused. The events or case reports which were confirmed by healthcare professional were considered for evaluation. Case listings were retrieved from the safety database and analysed for evaluation.

**Results**: During this study period 310 escitalopramcases were analysed and 841 events were found. Of these 37 (4.39%) events were reported by HCP, with both the SOCs (a&b). whereas 26 (70.27%) for congenital, familial and genetic disorders and 11 (29.72%) for pregnancy, puerperium and perinatal conditions.

**Conclusion**: At this point of time by considering congenital, familial and genetic disorders and safety in pregnancy, we measured risk benefit balance of escitalopramis favourable and routine risk minimization measures are sufficient for these risks.

**Key words:** Escitalopram, Congenital, Genetic disorders,Pregnancy**.**

**Introduction**: Escitalopram has been available since 2003 for the treatment of major depression, panic disorders, social phobia and generalized anxiety disorder[1]. Pregnant women with psychiatric illnesses are often treated with antidepressant drugs. As an example, studies of pregnant women in Europe have found that antidepressants were used by approximately 3% and in the United States by 8%. The most commonly used and studied drugs are Selective Serotonin Reuptake Inhibitors (SSRIs). Antidepressants cross the placenta and foetal blood brain barrier. Prenatal exposure thus involves potential risks of teratogenesis, preterm birth, low birth weight and pregnancy complications (eg, spontaneous abortion and postpartum haemorrhage), as well as postnatal effects (eg, persistent pulmonary hypertension of the new-born)[2]. The main focus of the safety monitoring activityis collection, assessment and reporting of the adverse drug reactions ofthe medicinal products. Globalization of the pharmaceutical industry has prompted efforts toward harmonization of safety monitoring

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practices worldwide to enable improved knowledge of medicine's benefit‑risk profile and risk communication/minimization.

Compared with the controls, higher risks were reported in new-borns of pregnant women using any antidepressant or tricyclic antidepressants in a limited number of studies. Exposure to antidepressants in the third trimester of pregnancy appeared to be associated more with neonatal seizures compared with earlier exposure[3]. There is a risk of congenital heart disease in patients who are prenatally exposed to anti-depressant medications as evident by the specific echocardiographic abnormalities noted in the study[4]. Previous studies have examined if maternal antidepressant medication during pregnancy increase the risk of autism spectrum disorder (ASD) in the offspring, but the results have been conflicting[5].

Escitalopram is an antidepressant belonging to a group of drugs called Selective Serotonin Reuptake Inhibitors (SSRIs). The use of SSRI and other anti-depressants during pregnancy is associated with many foetal abnormalities and birth defects. Between 2 to 10% of pregnant women are treated with selective serotonin-reuptake inhibitors (SSRIs) for depression[6].

For escitalopram only limited clinical data are available regarding exposed pregnancies. Animal studies have shown reproductive toxicity. Escitalopram should not be used during pregnancy unless clearly necessary and only after careful consideration of the risk/benefit. Neonates should be observed if maternal use of escitalopram continues into the later stages of pregnancy, particularly in the third trimester. Abrupt discontinuation should be avoided during pregnancy.

According to originator product label of escitalopram, the following symptoms may occur in the neonate after maternal SSRI/SNRI (Serotonin-norepinephrine reuptake Inhibitor) use in later stages of pregnancy: respiratory distress, cyanosis, apnoea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycaemia, hypertonia, hypotonia, hyperreflexia, tremor, jitteriness, irritability, lethargy, constant crying, somnolence and difficulty sleeping. These symptoms could be due to either serotonergic effects or discontinuation symptoms. In a majority of instances, the complications begin immediately or soon (<24 hours) after delivery. Nowadays, the selective serotonin reuptake inhibitor, escitalopram is considered to be one of the most effective and well tolerated agents for the treatment of moderate and severe major depressive disorder, as well as for the treatment of anxiety disorders[7].

**Materials and Methods**: Cumulative data of ICSRs received from different sources from 2014 to 2018 were studied. All adverse events (AEs) from valid cases from spontaneous and published literature sources were considered for this evaluation. Case listings were retrieved from the safety database for evaluation. Only Health care professional (HCP) cases or HCP reported AEs received from spontaneous (Health authority, Health care professional) and literature source (PubMed and Reactions Pharmacovigilance Insight) was considered for this evaluation. The AEs reported to the SOCs (System Organ Class), (a) congenital, familial and genetic disorders and (b) pregnancy, puerperium and perinatal conditions were focused. Retrieved case listings were assessed for the data related of both SOCs.Seriousness of the events was not measuredseparately, as all events related to both the mentioned SOCs were considered as medically important and safety wise significant.

Limitations of this study are mentioned below:

- Only adult pregnant patients have been considered.
- Duration taken from 2014-2018

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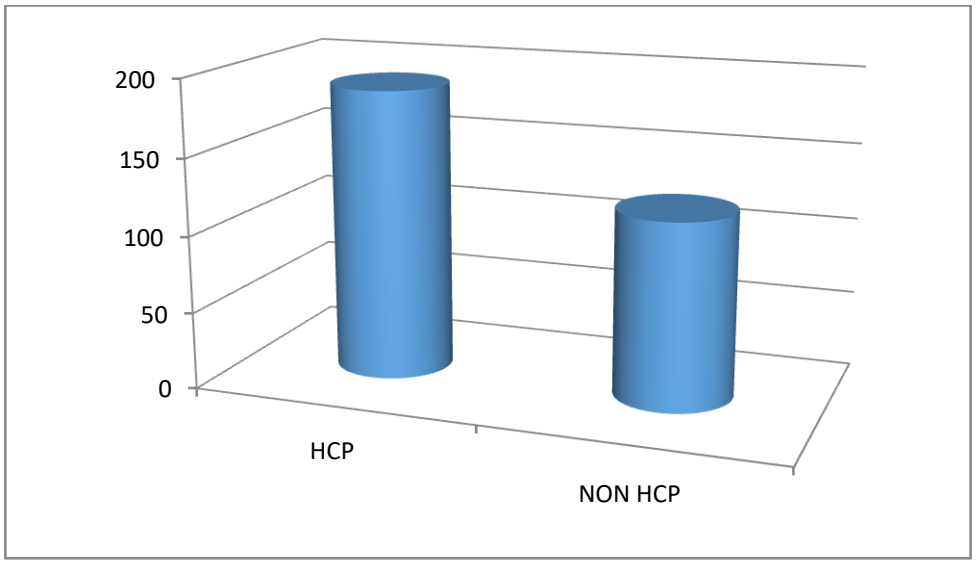
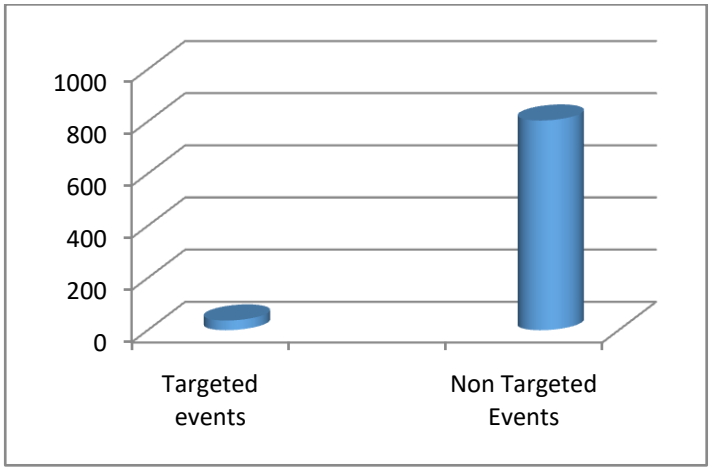
- AEs caused due to SSRI in different country population
- AEs with different indication
- Event classification as per SOC (System Organ Classification)
- Only spontaneous/literature cases
- Only valid cases
- HCP confirmed cases

**Results**: During this five years period a total of 310 escitalopram cases were received. Of these 310 escitalopram cases, 189 (61%) reported by HCP and remaining 121 (39%) reported by Non HCP. Fig: 1




During the study period for 310 cases of escitalopram, 841 events were reported or received from different sources. Of these 37 (4.39%) events were reported with both the SOCs (a & b)i.e. the targeted events (Table 1) and remaining 804 events were non targeted events. Fig: 2




A total of 26 (70.27%) events were for SOC (a) congenital, familial and genetic disorders and remaining SOC (b) 11 (29.72%)were for pregnancy, puerperium and perinatal conditions. Fig: 3

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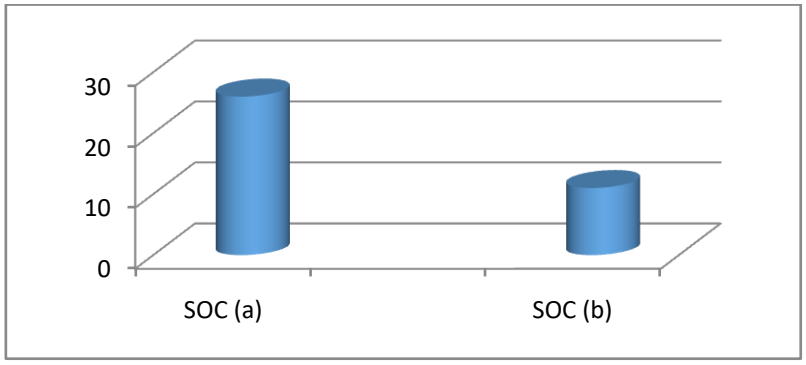


Most commonly/frequently reported adverse event was atrial septal defect and small for dates baby underthe SOC (a) congenital, familial and genetic disorders and (b) pregnancy, puerperium and perinatal conditions respectively as shown in below figures.

**Table 1: Events(Preferred Term) arrangement by System organ class (SOC)**

| **System organ class (SOC) a & b**<br>**Event Preferred Term** | **Count of Event Preferred Term (N)** |
|---|---|
| **Congenital, familial and genetic disorders SOC (a)** | **26** |
| Anencephaly | 1 |
| Atrial septal defect | **4** |
| Congenital hydronephrosis | 1 |
| Congenital megaureter | 1 |
| Congenital nose malformation | 1 |
| Congenital pulmonary hypertension | 1 |
| Congenital tricuspid valve incompetence | 1 |
| Cryptorchism | 1 |
| Cystic fibrosis | 1 |
| Developmental hip dysplasia | 1 |
| Dextrocardia | 1 |
| Encephalocele | 1 |
| Hypospadias | 2 |
| Kidney duplex | 2 |
| Pelvic kidney | 1 |
| Pulmonary artery stenosis congenital | 2 |
| Renal dysplasia | 1 |
| Truncusarteriosus persistent | 1 |
| Ventricular septal defect | 2 |

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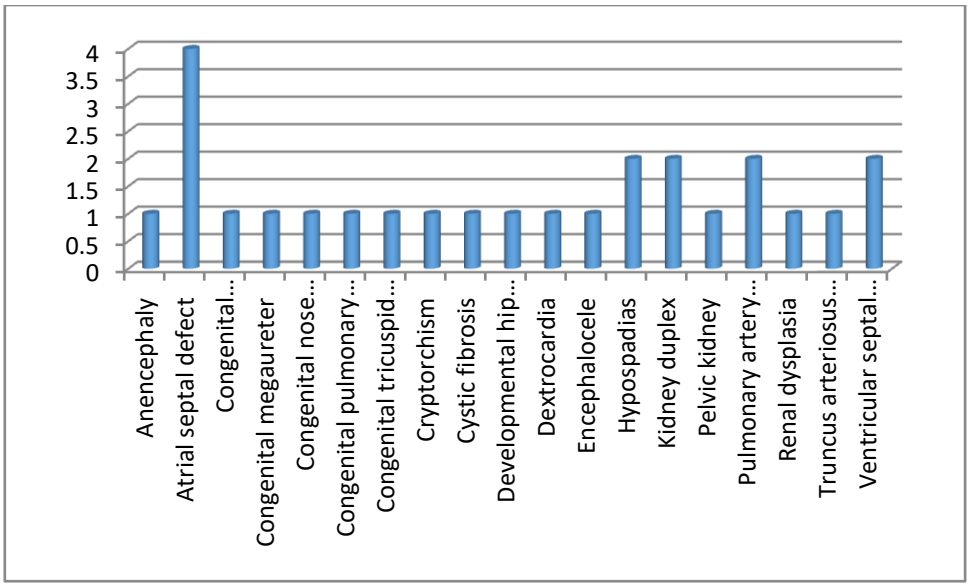
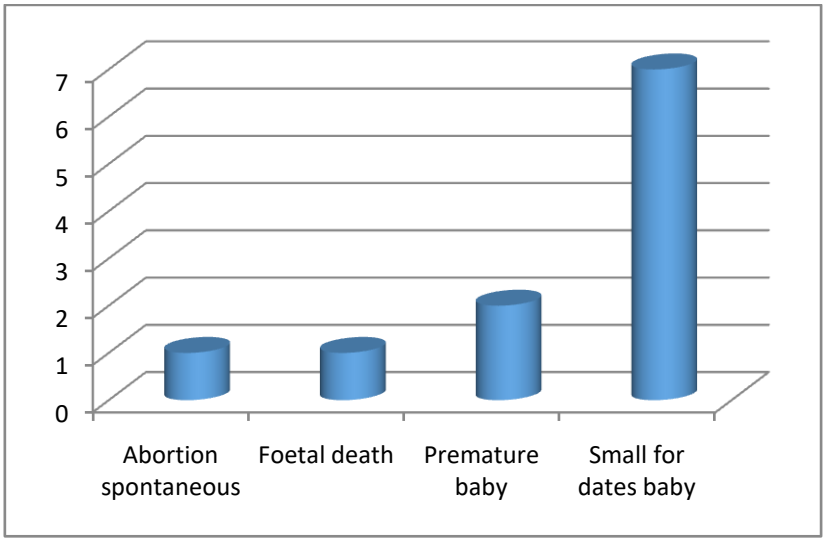
| **Pregnancy, puerperium and perinatal conditions SOC (b)** | **11** |
|---|---|
| Abortion spontaneous | 1 |
| Foetal death | 1 |
| Premature baby | 2 |
| Small for dates baby | 7 |
| **Grand Total** | **37** |

**N= number of times event occurred.**

As per the above mentioned table, frequency of events under SOC (a) is as follows. Fig: 4




As per the above mentioned table, frequency of events under SOC (b) is as follows. Fig: 5



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**Discussion:** The safety profile of escitalopram during the gestational period is an important topic for the health care community because the prescription of such drugs during pregnancy and in women of childbearing age affected by psychiatric illnesses is still up for debate. There is still some uncertainty about the relative risk concerning the use of escitalopram in pregnancy, as data on its safety are available only after the drug has been prescribed for many years. On the other hand, it is well documented that untreated maternal major depressive disorder and/or anxiety disorders, as well as other severe psychiatric illnesses, can have disruptive consequences on the outcome of pregnancy and on the safety of the new born.

Seven cases were received for Small for dates baby and escitalopram was taken for entire pregnancy. Of these seven cases four were taken for depression, two were taken for anxiety disorder and in one case indication was not reported. Average age of the mother was 30 years and all patients were take dosage at the limits of prescribed dosage.

Four cases were received for Atrial septal defect and except in one case (unknown) escitalopram was taken entire pregnancy. Of these four cases two were taken for Depression, two were taken for Anxiety disorder. Average age of the mother was 32 years and all patients were take dosage at the limits of prescribed dosage. The details of the individual cases were presented in Table 2.

**Table 2: Details of the cases reported**

| Event | Time of exposure in pregnancy | Indication | Dosage | Mother age |
|---|---|---|---|---|
| **Small for dates baby** | Entire pregnancy | Unknown | 10 mg/daily | 27-years |
| | Entire pregnancy | Anxiety disorder | 10 mg/daily | 27-years |
| | Entire pregnancy | Depression | 10 mg/daily | 27-years |
| | Entire pregnancy | Anxiety disorder | 25 mg/daily | 27-years |
| | Entire pregnancy | Depression | 20 mg/daily | 33-years |
| | Entire pregnancy | Depression | 15 mg/daily till third trimester, then 5 mg/daily | 34-years |
| | Entire pregnancy | Depression | 10 mg/daily | 34-years |
| **Atrial septal defect** | Entire pregnancy | Anxiety disorder | 20 mg/daily | 40-years |
| | Entire pregnancy | Anxiety disorder | 20 mg/daily | 40-years |
| | Entire pregnancy | Depression | 22.5mg/Daily | 28-years |
| | Unknown | Depression | 10 mg/daily | 21-years |

**Events reported: Small for dates baby and a trial septal defect**

Small for dates baby and atrial septal defect both were most occurring events with escitalopram. Both were serious and unlabelled for escitalopram. Remaining all other events are reported in singular or less frequently reported and all reported events are unexpected with escitalopram. The evidence suggests a generally small risk of congenital malformations and argues against a substantial teratogenic effect of SSRIs. Caution is advisable in making decisions about whether to continue or stop treatment with SSRIs during pregnancy[8]. Limited assessment was made due to lack of information in few reports (trimester exposed outcome and event latency).

**Conclusion**: Escitalopram should be prescribed in pregnancy with caution and risk; benefit balance can be measured before prescribing. Choice of other anti-depressants also needs to be taken in to consideration, due to its congenital and pregnancy issues. It is important that health care professionals treating fertile women with a psychiatric disease should discuss whether psychotropic drugs are needed during pregnancy and how it has to be administered[9]. Careful and periodic monitoring is compulsory required for those who have exposure to escitalopram during pregnancy. At this point of time by considering its congenital, familial and genetic disorders and safety in pregnancy, we measured risk benefit balance is favourable and routine risk minimization measures are sufficient for this risks.

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**Conflicts of interest**

The authors declare that there are no conflicts of interest.

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