



MHRA UK PUBLIC ASSESSMENT REPORT

Fluoxetine: may slightly increase risk of heart defects in an unborn child if taken during pregnancy

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PLAIN-LANGUAGE SUMMARY

KEY MESSAGE: Taking the antidepressant medicine fluoxetine in the first three months of pregnancy may cause a small increase in the risk of heart defects in the unborn child. The background incidence of this condition is approximately 1 per 100 pregnancies; the risk of heart defects in an unborn child after fluoxetine use during pregnancy is in the region of 2 per 100 pregnancies.

Background

The Medicines and Healthcare products Regulatory Agency (MHRA) is the government agency responsible for regulating medicines and medical devices in the UK. We continually review the safety of medicines and vaccines in the UK, and inform healthcare professionals and the public of the latest updates through several means, including public assessment reports. This report discusses an analysis of the scientific and clinical evidence that taking a medicine called fluoxetine during pregnancy may increase the risk of heart defects in the unborn child.

Fluoxetine (brand names Prozac and Oxactin) is a commonly used prescription medicine for the treatment of depression,^a which belongs to the selective serotonin reuptake inhibitor (SSRI) class of medicines. Depression occurs widely in many populations including pregnant women, of whom 7–20% are estimated to experience depressive symptoms or disorders. Untreated depression in pregnancy can lead to a variety of clinical problems in both the mother and the newborn baby, so it is important that depression in pregnancy is treated effectively and safely.

A US study showed that around 2% of pregnant women use SSRI antidepressant medicines. However, as with any medicine, the use of SSRIs may lead to suspected adverse drug reactions (ADRs; side effects) in some individuals. Evidence from published clinical studies suggests an association between the use of the SSRI fluoxetine in the first trimester^b of pregnancy, and a small increase in the risk of congenital cardiac defects (heart defects in the unborn child). This risk was already communicated for another SSRI, paroxetine, in 2005 (see [MHRA safety warning, December 2005](#)). To assess the risk of congenital cardiac defects associated with fluoxetine use in pregnancy, the MHRA and a European committee called the [Pharmacovigilance Working Party](#)^c reviewed the data from an analysis of published studies on this topic. The results and conclusions from this analysis are summarised below.

Results

Seven published clinical studies were identified which examined the risk of defects occurring in an unborn child with the use of fluoxetine during the first trimester of pregnancy. These data suggest that fluoxetine was not associated with non-cardiac congenital defects (odds ratios^d and 95% confidence intervals^e: 1.08 [0.84–1.39]).

^a A clinical mental health disorder characterised by symptoms such as depressed mood, loss of interest or pleasure in life, and disturbed sleep and appetite. The condition can become chronic or recurrent, and substantially impair everyday life.

^b Periods of three months into which a pregnancy can be divided

^c A group which provides recommendations on pharmacovigilance matters to the Committee for Medicinal Products for Human Use in the European Medicines Agency

^d A measure of risk for one group compared to another. A value close to or equal to 1 suggests no change in risk. A value greater than 1 suggests an increased risk.

^e Difference in risk between two groups

However, cardiac defects were reported in five of these seven studies. Analysis of data from these five studies suggests that fluoxetine is associated with a small increased risk of cardiac congenital defects (odds ratio and 95% confidence intervals: 1.43 [0.83–2.47]).

The background (naturally occurring) incidence/risk of congenital cardiac defects is approximately 1 per 100 pregnancies. The results suggest that the risk of this condition with the use of fluoxetine in pregnancy is in the region of 2 per 100 pregnancies, which is similar to the risk seen with paroxetine. The mechanism of this risk is unknown and it is possible that these effects may be associated with other SSRIs; however, available data at present are insufficient to draw conclusions for other medicines in this class.

Conclusions

- Use of the SSRI antidepressant fluoxetine in early pregnancy may cause a small increased risk of heart defects in the unborn child. This is similar to the risk seen with another SSRI, paroxetine.
- There are insufficient data at present to conclude whether there is a similar risk with other SSRIs.

The above information has been communicated in an article in the [March 2010 issue of Drug Safety Update](#), the monthly MHRA publication containing the latest information and advice on medicines and vaccines safety. On the basis of the results of the analysis, the following warnings on the risk of congenital cardiac defects were included in the product information (Summary of Characteristics^a [SPC]) and Patient Information Leaflets [PILs] for all medicines containing fluoxetine:

Fluoxetine SPC wording

Section 4.6 Pregnancy and lactation

Pregnancy: Some epidemiological studies suggest an increased risk of cardiovascular defects associated with the use of fluoxetine during the first trimester. The mechanism is unknown. Overall the data suggest that the risk of having an infant with a cardiovascular defect following maternal fluoxetine exposure is in the region of 2/100 pregnancies, compared with an expected rate for such defects of approximately 1/100 pregnancies in the general population.

Fluoxetine PIL wording

Pregnancy and breast-feeding

Pregnancy. Talk to your doctor as soon as possible if you're pregnant, if you might be pregnant, or if you're planning to become pregnant.

^a Detailed information that accompanies every licensed medicine, listing its composition and characteristics, which is available on the electronic Medicines Compendium website: <http://www.medicines.org.uk/emc/>

In babies whose mothers took fluoxetine during the first few months of pregnancy, there have been some reports suggesting an increased risk of birth defects affecting the heart. In the general population, about 1 in 100 babies are born with a heart defect. This increased to about 2 in 100 babies in mothers who took fluoxetine. You and your doctor may decide that it is better for you to gradually stop taking fluoxetine while you are pregnant. However, depending on your circumstances, your doctor may suggest that it is better for you to keep taking fluoxetine.

1. INTRODUCTION

(See glossary for an explanation of terms used in this report)

The Medicines and Healthcare products Regulatory Agency (MHRA) is the government agency responsible for regulating medicines and medical devices in the UK. We continually review the safety of medicines and vaccines in the UK, and inform healthcare professionals and the public of the latest updates through several means, including public assessment reports. The following report summarises an analysis of evidence on the association between fluoxetine use in the first trimester of pregnancy, and the risk of congenital malformations.

2. BACKGROUND

Selective serotonin reuptake inhibitors are commonly prescribed for the treatment of major depression. This condition affects many individuals in the UK, including around 7–20% of pregnant women^[1,2]. Untreated depression in pregnancy can lead to a variety of adverse outcomes for the newborn including low birth weight, preterm delivery, and lower Apgar scores^[3,4], and problems for the mother including the risk of self-harm, so it is important that pregnant women who suffer from depression receive appropriate treatment

A US study showed that around 2% of pregnant women use SSRI antidepressant medicines^[4]. However, as with any medicine, the use of SSRIs may cause adverse drug reactions (ADRs) in some individuals. Evidence from published clinical studies has suggested an association between the use of the SSRI fluoxetine in the first trimester of pregnancy, and a small increase in the risk of congenital cardiac defects. This risk has already been identified with another SSRI, paroxetine, in 2005. At this time, following an analysis of available data, the MHRA issued the following warning: “Taking paroxetine in early pregnancy may increase the risk of cardiac congenital defects from a background incidence of 1 per 100 babies to approximately 2 per 100 babies” (see [MHRA safety warning, December 2005](#)).

To assess the risk of congenital cardiac defects associated with fluoxetine use in pregnancy, the MHRA and the European [Pharmacovigilance Working Party](#)^a have reviewed the data from an analysis of published studies on this topic. The results and conclusions from this analysis are summarised below.

^a A group which provides recommendations on pharmacovigilance matters to the Committee for Medicinal Products for Human Use in the European Medicines Agency

3. DATA CONSIDERED

An analysis was performed of data from seven studies which assessed the association between fluoxetine exposure in the first trimester of pregnancy and the risk of all congenital defects (table 1). Five of these seven studies reported cardiac defects, therefore an additional analysis of data from these five studies was performed to assess the association between fluoxetine exposure in the first trimester, and cardiac congenital defects only (table 2).

Table 1. Risk of all major congenital defects in babies born to women exposed to fluoxetine in first trimester of pregnancy

Study	Odds ratio (95% CI)	p-value
Einarson et al, 2009 ^[5]	1.87 (0.55–6.37) [compared to no use of fluoxetine]	p=0.318
Diav-Citrin et al, 2008 ^[6]	1.94 (0.99–3.80) [compared to no use of fluoxetine]	p=0.053
Chambers et al, 1996 ^[7]	1.40 (0.54–3.61) [compared to no use of fluoxetine]	p=0.486
Pastuszek et al, 1993 ^[8]	1.13 (0.16–8.14) [compared to no use of fluoxetine, and use of tricyclic antidepressants]	p=0.907
Oberlander et al, 2008 ^[9]	1.05 (0.68–1.63) [compared with no use of fluoxetine]	p=0.822
Malm et al, 2005 ^[10]	1.66 (1.02–2.71) [compared to no use of fluoxetine]	p=0.041
Källén and Otterblad Olausson, 2007 ^[11]	0.82 (0.59–1.14) [compared to background incidence of congenital defects]	p=0.234
ALL	1.08 (0.84–1.39)	p=0.456

CI=confidence interval

Table 2. Risk of cardiovascular congenital defects only, in babies born to women exposed to fluoxetine in first trimester of pregnancy

Study	Odds ratio (95% CI)	p-value
Diav-Citrin et al,	4.81 (1.73–13.37)	p=0.003

2008 ^[6]	[compared to no use of fluoxetine]	
Chambers et al, 1996 ^[7]	4.19 (0.43–40.67) [compared to no use of fluoxetine]	p=0.216
Pastuszak et al, 1993 ^[8]	0.56 (0.05–6.24) [compared to no use of fluoxetine, and tricyclic antidepressants]	p=0.635
Oberlander et al, 2008 ^[9]	1.65 (0.68–3.99) [compared with no use of fluoxetine]	p=0.268
Källén and Otterblad Olausson, 2007 ^[11]	1.00 (0.57–1.77) [compared to background incidence of congenital defects]	p=1.00
ALL	1.43 (0.83–2.47)	p=0.143

CI=confidence interval

Although most of the results from these studies did not reach statistical significance, the overall weight of the evidence suggests that use of fluoxetine in the first trimester of pregnancy is associated with a small increased risk of cardiac congenital defects. The results also suggest that fluoxetine use in the first trimester of pregnancy is not associated with a risk of non-cardiac defects, and that any overall increased risk of defects is driven by an increase in cardiac risk. The cardiac defects reported in the studies varied, ranging from reversible ventricular septal defects to transposition of the great vessels.

4. DISCUSSION

The analysis provides a combined risk estimate of: 1.08 (0.84–1.39) for all congenital defects, and 1.43 (0.83–2.47) for cardiovascular congenital defects only, associated with fluoxetine use during early pregnancy. Any increased risk of all defects appears to be driven by the excess cardiovascular risk.

All studies in the analysis had several important limitations. These include: a lack of information about timing, dose and duration of fluoxetine use; a reliance on medication history as reported by the mother at the first antenatal visit and a lack of detailed information about the underlying condition for which fluoxetine was taken.

However, several of the studies were large and well-conducted, and the results provide a risk estimate for fluoxetine that is derived from a data set comparable to the risk estimate already established for paroxetine.

The background incidence/risk of congenital cardiac defects is approximately 1 per 100 pregnancies. The results suggest that the risk of this condition with maternal fluoxetine use is in the region of 2 per 100 pregnancies, which is similar to the risk seen with paroxetine. The mechanism of this risk is unknown and it is possible that these effects may be associated with other SSRIs; however available data at present are insufficient to draw conclusions for other medicines in this class.

5. CONCLUSIONS AND ACTIONS

An analysis of available data has provided evidence that there is a risk of cardiovascular defects in infants whose mothers were exposed to fluoxetine in the first trimester of pregnancy. The analysis does not provide evidence of an association between non-cardiovascular defects and exposure to fluoxetine in the first trimester.

Summary:

- Use of the SSRI antidepressant fluoxetine in early pregnancy may cause a small increased risk of heart defects in the unborn child. This is similar to the risk seen with another SSRI, paroxetine.
- There are insufficient data at present to conclude whether there is a similar risk with other SSRIs.

This information was communicated in an article in the [March 2010 issue of Drug Safety Update](#), the monthly MHRA publication containing the latest information and advice on medicines and vaccines safety. On the basis of the results of the analysis, a warning on the risk of congenital cardiac defects was included in the product information (Summary of Characteristics^a [SPC]) and Patient Information Leaflets [PILs]) for all medicines containing fluoxetine:

Fluoxetine SPC wording

^a Detailed information that accompanies every licensed medicine, listing its composition and characteristics, which is available on the electronic Medicines Compendium website: <http://www.medicines.org.uk/emc/>

Section 4.6 Pregnancy and lactation

Pregnancy: Some epidemiological studies suggest an increased risk of cardiovascular defects associated with the use of fluoxetine during the first trimester. The mechanism is unknown. Overall the data suggest that the risk of having an infant with a cardiovascular defect following maternal fluoxetine exposure is in the region of 2/100 pregnancies, compared with an expected rate for such defects of approximately 1/100 pregnancies in the general population.

Fluoxetine PIL wording

Pregnancy and breast-feeding

Pregnancy: Talk to your doctor as soon as possible if you're pregnant, if you might be pregnant, or if you're planning to become pregnant.

In babies whose mothers took fluoxetine during the first few months of pregnancy, there have been some reports suggesting an increased risk of birth defects affecting the heart. In the general population, about 1 in 100 babies are born with a heart defect. This increased to about 2 in 100 babies in mothers who took fluoxetine. You and your doctor may decide that it is better for you to gradually stop taking fluoxetine while you are pregnant. However, depending on your circumstances, your doctor may suggest that it is better for you to keep taking fluoxetine.

6. REFERENCES

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7. GLOSSARY

ADRs (adverse drug reactions)

Side effects experienced with a medicine or vaccine

Apgar scores

A rating system used by clinicians to assess a baby's health

[Committee for Medicinal Products for Human Use](#)

(CHMP): A group of medical experts who are responsible for preparing opinions from the [European Medicines Agency](#) on all questions concerning medicines for human use

Confidence interval

A statistical range of numbers with a specific probability that a particular value lies within this range. Confidence intervals (CI) are used to assess the true difference in risk between two groups, and usually accompany ratio values such as **odds ratios**, hazard ratios and 'observed versus expected' ratios. A 95% CI suggests that there is a 95% chance that the real difference between two groups is within this interval. If a 95% CI does not cross 1, the ratio is regarded as statistically significant

Confounds/confounding/confounded

Where the presence of one **risk factor** changes the effects that another risk factor has on the development of a medical condition; this can affect the results of a study

Congenital

A medical condition that is acquired by the **fetus** during pregnancy and is present at birth

Defect

A fault or imperfection in the body

Depression

A clinical mental health disorder characterised by symptoms such as depressed mood, loss of interest or pleasure in life, and disturbed sleep and appetite. The condition can become chronic or recurrent, and substantially impair everyday life.

Epidemiological studies

Studies which assess trends in the occurrence, distribution or control of diseases or medical conditions in defined populations

[European Medicines Agency](#)

(EMA): The Agency responsible for the scientific evaluation and safety-monitoring of medicinal products in the European Union

Fetus

An unborn child developing in the mother's womb

Fluoxetine

An antidepressant medicine belonging to the **SSRI** drug class

Lactation

Production of milk by breasts, normally at the end of pregnancy

Odds ratio

A measure of risk for one group compared with another group. A value greater than 1 suggests an increased risk; a value equal to 1 suggests an equal risk; and a value

less than one suggests a decreased risk. Odds ratios are usually accompanied by a confidence interval (CI) – a statistical method of assessing the true difference in risk between the two groups. A 95% CI suggests that there is a 95% chance that the real difference between the two groups is within this interval. If a 95% CI does not cross 1, the odds ratio is regarded as statistically significant

Paroxetine

An antidepressant medicine belonging to the **SSRI** drug class

Pharmacovigilance

Identifying, assessing and responding to safety issues that emerge for medicines used in clinical practice

Pharmacovigilance Working Party

A group who provide recommendations on **pharmacovigilance** matters to the **Committee for Medicinal Products for Human Use** in the **European Medicines Agency**

p-value

A measure of the statistical probability of an event occurring by chance. Usually, a p-value of less than 0.05 suggests the event is statistically significant and did not occur by chance; a p-value of 0.05 or greater suggests the event is not statistically significant and occurred by random chance

Risk factor

A substance or activity that increases the likelihood of an individual developing an illness or medical condition

Selective serotonin reuptake inhibitor (SSRI)

A class of antidepressant drugs

Summary of Product Characteristics

Detailed information that accompanies every licensed medicine, listing its composition and characteristics, which is available at:

<http://www.medicines.org.uk/emc/>

Transposition of the great vessels

A group of **congenital** heart defects involving an abnormal arrangement of any of the major blood vessels in the developing **fetus**

Trimester

One of the three 3-month periods that a human 9-month pregnancy can be divided into

Ventricular septal defects

A defect (or damage) to the wall dividing the right and left chambers of the heart