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[Intervention Review]

Calcium channel blockers for potential impaired fetal growth

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ABSTRACT

Background

Calcium channel blockers may increase the blood flow to the fetus or may improve fetal-placental cellular energy generation. This could enhance fetal growth.

Objectives

The objectives of this review were to assess the effects of calcium channel blockers on fetal growth and neonatal morbidity and mortality in pregnancies where impaired fetal growth is suspected.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (June 2009).

Selection criteria

Acceptably controlled trials of calcium channel blockers in women with potential impaired fetal growth.

Data collection and analysis

Eligibility and trial quality were assessed.

Main results

One study of 100 women (all smokers) was included. Mean birthweight was significantly higher in women receiving flunarizine compared to the control group. No other significant differences were found.

Authors' conclusions

There is not enough evidence to evaluate the use of calcium channel blockers for impaired fetal growth. The apparent beneficial effect of calcium channel blockers on birthweight warrants further investigation.

PLAIN LANGUAGE SUMMARY

Calcium channel blockers for potential impaired fetal growth

Too little evidence to show whether the unborn baby's growth improves when pregnant women take calcium channel blockers, and more research is needed.

Calcium channel blocker drugs relax muscles and lower blood pressure by reducing the intake of calcium into some cells. It has been thought that these drugs may improve the growth of an unborn baby who is growing more slowly than expected in the womb (impaired fetal growth). The review of trials has found too little evidence from trials on the effects of pregnant women taking calcium channel blockers. Only one trial, involving 100 women, has been included. However, there is some evidence of improved growth in some babies, and more research is needed into the effects of these drugs on both smoking and non-smoking women and their babies.

BACKGROUND

Impaired fetal growth is the failure of a newborn to achieve its genetically determined growth potential, which may cause death as well as short or long-term childhood morbidity. It has been reported that 3% to 10% of neonates are small for corresponding gestational age and an estimated 30% of this is due to impaired fetal growth. Remaining 70% is due to constitutional factors such as maternal ethnicity, parity, weight and height (Lin 1998). The condition occurs with limited flow of nutrients and/or oxygen from mother to fetus as a result of fetal causes (e.g. chromosomal abnormalities, congenital malformations), placental factors (e.g. small placenta), or maternal factors (e.g. malnutrition, vascular/renal disease, drugs or other metabolic conditions) (Resnik 2002).

Ultrasound evaluation of the fetus by measuring the abdominal circumference, head circumference, length of upper leg and interpreting these using standardised formulae allows the clinician to estimate the fetal weight, to relate this to the gestational age and to follow the growth progress. Ultrasound evaluation also allows to some extent to estimate the timing and the cause of the impairment. Symmetrical growth of the fetus is generally due to early problems such as chromosomal abnormalities, drugs, chemical agents or infection. Asymmetric growth usually results from inadequacy of substrates the fetus needs particularly later in pregnancy (Resnik 2002). In low-income settings where early pregnancy ultrasound is not available fetal growth can be monitored by serial symphysis fundus measurements. However, there is no proven effective treatment that can be applied once growth impairment is diagnosed. In general, when no apparent congenital abnormality exists, management is conservative by frequent growth measurements, smoking cessation if the mother smokes and early delivery when the fetus is thought be mature enough to survive outside the womb.

The outcomes of impaired growth are variable and usually related to the specific cause. For example, if the growth impairment is due to chromosomal anomalies or congenital abnormalities, the fetus is more at risk of a perinatal death. Other short-term outcomes may be moderate to mild metabolic problems (hypoglycemia, polycythemia, meconium aspiration, etc.) due to the chronic oxygen and nutrient deprivation. Depending on the severity and the duration of the condition, long-term outcomes may differ from normal to small decreases in IQ to an increased risk of cerebral palsy (Bernstein 2000).

Calcium channel blockers have effects on vascular contractility as well as intracellular energy generation by blocking calcium entry into the cell. Various calcium channel blockers with differential effects are available. Nimodipine has been shown to reduce resistance to blood flow in the cerebral arteries in a series of 10 women with pre-eclampsia (Belfort 1994). Calcium channel blockers have also been researched as tocolytic agents in addition to their main use which is lowering of blood pressure. Therefore, there is a theoretical possibility of increasing blood flow to the fetus or improving fetoplacental cellular energy generation which could result in improved outcomes for fetuses with growth impairment.

OBJECTIVES

To assess the effects on fetal and neonatal morbidity and mortality of calcium channel blockers in pregnancies with increased potential for impaired fetal growth.

METHODS

Criteria for considering studies for this review

Types of studies

All acceptably controlled trials of calcium channel blockers in potential impaired fetal growth.

Types of participants

Women either at high risk or with suspected impaired fetal growth.

Types of interventions

Calcium channel blockers.

Types of outcome measures

Fetal growth, perinatal mortality, neonatal morbidity, neonatal anthropometric measurements.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (June 2009).

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE;
3. handsearches of 30 journals and the proceedings of major conferences;
4. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL and MEDLINE, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the [Cochrane Pregnancy and Childbirth Group](#).

Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

We did not apply any language restrictions.

Data collection and analysis

Trials under consideration were evaluated for methodological quality and appropriateness for inclusion, without consideration of their results. A quality score for concealment of allocation was assigned to each trial using the criteria described in [Clarke 2000](#):

- (A) adequate concealment of the allocation;
- (B) unclear whether adequate concealment of the allocation;
- (C) inadequate concealment of allocation;
- (D) no concealment of allocation.

Whether or not an 'intention-to-treat' analysis was done in the primary study was examined. There were no language preferences in the review.

Included trial data were extracted and processed as described in [Clarke 2000](#).

RESULTS

Description of studies

See '[Characteristics of included studies](#)'.

Risk of bias in included studies

In the study of Janssens ([Janssens 1985](#)), participants were 'randomly assigned' to flunarizine or matching placebo. There was an unexplained imbalance in the infant sex ratio (18 males: five females in the study group versus 11 males: 13 females among the controls) in the interim analysis. This discrepancy did not persist in the final analysis (27 males: 23 females versus 26 males: 24 females).

Effects of interventions

Among 50 women who received 10 mg flunarizine daily, the mean duration of pregnancy was 282 days, versus 279 days in the placebo group ($n = 50$, $P = 0.2$). The mean birthweight was greater in the study group (3291 g versus 3011 g in the placebo group, $P = 0.0024$).

The lower incidence of preterm births may reflect the play of chance, as may the difference in perinatal mortality.

DISCUSSION

Calcium channel blockers have diverse effects. They may improve intracellular energy generation and decrease smooth muscle contractility. The trial reviewed is sufficiently encouraging to justify further research in this area. However, only smoking women with impaired fetal growth were included in this trial and it would be worthwhile exploring whether this effect is seen only in this group of women.

AUTHORS' CONCLUSIONS

Implications for practice

There is inadequate evidence from this trial to support the routine use of calcium channel blockers in pregnancies in which the risk of impaired fetal growth is increased.

Implications for research

The results of this small trial are sufficiently encouraging to justify further trials with sufficient numbers and inclusion of both smoking and nonsmoking women with impaired fetal growth to assess effects on substantive outcomes.

ACKNOWLEDGEMENTS

None.

REFERENCES

References to studies included in this review

Janssens 1985 {published and unpublished data}

Janssens D. Prevention of low birth weight by flunarizine given to smoking mothers. *Archives of Gynecology* 1985;**237**(Suppl 1):397.

References to studies excluded from this review

Rizzo 1987 {published data only}

Rizzo G, Arduini D, Mancuso S, Romanini C. Effects of nifedipine on umbilical artery velocity waveforms in healthy human fetuses. *Gynecologic and Obstetric Investigation* 1987;**24**:151-4.

Additional references

Belfort 1994

Belfort MA, Saade GR, Moise KJ Jr, Cruz A, Adam K, Kramer W, et al. Nimodipine in the management of preeclampsia: maternal and fetal effects. *American Journal of Obstetrics and Gynecology* 1994;**171**:417-24.

Bernstein 2000

Bernstein IM, Horbar JD, Badger GJ, Ohlsson A, Golan A. Morbidity and mortality among very low birth weight infants with intrauterine growth restriction. The Vermont Oxford Network. *American Journal of Obstetrics and Gynecology* 2000;**182**:198.

Clarke 2000

Clarke M, Oxman AD, editors. Cochrane Reviewers' Handbook 4.1 [updated June 2000]. In: Review Manager (RevMan) [Computer program]. Version 4.1. Oxford, England: The Cochrane Collaboration, 2000.

Lin 1998

Lin C, Santolaya-Forgas J. Current concepts of fetal growth restriction: Part 1. Causes, classification, and pathophysiology. *Obstetrics & Gynecology* 1998;**92**(6):1044-55.

Resnik 2002

Resnik, R. Intrauterine growth restriction. *Obstetrics & Gynecology* 2002;**99**(3):490-6.

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Janssens 1985

Methods	The participants were randomly assigned to double-blind treatment. The method of randomization is not described.
Participants	100 smoking pregnant women at 16 to 20 weeks of gestation (50-study, 50-control).
Interventions	10 mg flunarizine or placebo daily given orally from 16-20th week until delivery.
Outcomes	Preterm birth (< 38 weeks). Mean birthweight. Duration of pregnancy. Perinatal mortality.
Notes	No standard deviations are given with continuous data.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Rizzo 1987	No clinical outcomes were given (when compared with placebo-treated controls, nifedipine 10 mg sublingually given to healthy women at 26 to 28 weeks' gestation caused a significant fall in umbilical artery pulsatility index lasting 90 minutes).

DATA AND ANALYSES

Comparison 1. Flunarizine versus no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Preterm birth (< 38 weeks)	1	100	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.50 [0.18, 1.40]
2 Perinatal mortality	1	100	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.14 [0.00, 6.82]

Analysis 1.1. Comparison 1 Flunarizine versus no treatment, Outcome 1 Preterm birth (< 38 weeks).

Analysis 1.2. Comparison 1 Flunarizine versus no treatment, Outcome 2 Perinatal mortality.

WHAT'S NEW

Date	Event	Description
24 June 2009	New search has been performed	Search updated. No new trials identified.

HISTORY

Protocol first published: Issue 1, 1995

Review first published: Issue 1, 1995

Date	Event	Description
1 September 2008	Amended	Converted to new review format.
24 November 2006	New search has been performed	New studies sought but none found.
30 June 2004	New search has been performed	Search updated but no new trials identified.

CONTRIBUTIONS OF AUTHORS

Justus Hofmeyr wrote the original review for the Cochrane Pregnancy and Childbirth Database. Metin Gülmezoglu updated the review, and has been responsible for maintaining the review since 1995. Both review authors did the data extraction and contributed to the text of the review. Lale Say contributed to the recent update by checking the data entries and revising the text of the review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- University of the Witwatersrand, South Africa.
- UK Cochrane Centre, NHS R&D Programme, Oxford, UK.
- HRP - UNDP/UNFPA/WHO/World Bank Special Programme in Human Reproduction, Geneva, Switzerland.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Calcium Channel Blockers [*therapeutic use]; Fetal Growth Retardation [*drug therapy]; Flunarizine [therapeutic use]

MeSH check words

Female; Humans; Pregnancy