

Enalapril Prescription to Women of Childbearing Age as Risk Factor for Congenital Defects in the Argentine Primary Care Level

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SUMMARY

Background

Use of angiotensin-converting enzyme inhibitors (ACEIs) during the first trimester of pregnancy is associated with a 2.71-fold increase in the risk of major congenital malformations (MCMs), a matter of care as ACEIs are one of the most frequent medications prescribed.

Objective

To quantify the prescription of enalapril –an ACEI– provided by the Remediar Program in women of childbearing age, and to think about the possible number of MCMs that could be prevented.

Material and Methods

The study has two designs: 1. Ecological study with cross comparisons of diagnoses, prescriptions and beneficiaries of the prescriptions of the Remediar Program (secondary sources). Target population: women between 15 to 49 years, treated at 6000 health care centers in Argentina from 2005 to 2006, with diagnosis of hypertension and/or prescription of enalapril. 2. Evaluation of a counterfactual approach of the impact following the reduction of exposure to ACEIs in such population.

Results

From a total of 15,001,041 R-Forms recorded during the year of the study, 2,085,338 women of childbearing age were identified; 5.5% of them received enalapril. Thus, considering that the number of MCMs expected using another medication would be 214 (95% CI 199-229) and the use of enalapril would increase the number of events to 579 (95% CI 296-863), the reduction of the exposure would prevent about 365 (95% CI 97-634) cases of MCD/year in the population covered by the Remediar Program.

Conclusions

Prescription of ACEIs in women of childbearing age is frequent. A significant number of cases of MCMs would be prevented avoiding the prescription and use of ACEIs in this population. More evidence is needed to evaluate this risk.

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Key words

> Enalapril - Congenital defects - Use of medications - Prevention

Abbreviations

>	CHD	Congenital heart defect	MCM	Major congenital malformation
	HT	Hypertension	WHO	World Health Organization
	ACEI	Angiotensin-converting enzyme inhibitor	SINTyS	Sistema de Identificación Nacional Tributario y Social

BACKGROUND

Major congenital malformations (MCMs) are the main cause of infant mortality in the United States and in developed countries. (1) Congenital heart defects (CHDs) produce 30% of deaths due to MCMs and 4% of all fetal deaths. (2, 3) According to the information provided by the Ministry of Health, of 700,000 children born in Argentina each year, 6,100 have CHDs: 70% need surgery, 50% are defects of high complexity and

25% should be operated on before the age of 28 days of life. (4)

The results of a recent study evaluating the exposure to angiotensin-converting enzyme inhibitors (ACEIs) during the first trimester of pregnancy and the association with MCMs are a matter of care, (5) as ACEIs are one of the most frequent medications prescribed for the treatment of hypertension (HT). (6) The study, conducted on a cohort of 29,507 infants,

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was well designed, with adequate control of selection, information and confusion biases, and demonstrated a statistically significant association for any MCM (RR, 2.71; 95% CI, 1.72 to 4.27) that was not found with other antihypertensive agents. The authors found increased risks of malformations of the cardiovascular system (RR, 3.72; 95% CI, 1.89 to 7.30) and the central nervous system (RR, 4.39; 95% CI, 1.37 to 14.02). In contrast, the risk of malformations was not increased in infants with exposure to other antihypertensive medications as compared with those with no fetal exposure to any hypertensive medications (RR, 0.66; 95% CI, 0.25 to 1.75). Exposure to ACEIs during the first trimester, which seemed to be safe compared to exposure during the second and third trimester of pregnancy, (7, 8) increased the probability of fetal MCMs from 2.63% to 7.12%. The strength of this statistically significant and valid association, the presence of temporality, specificity and biological plausibility, are all criteria to establish causality. (9)

The study by Cooper arises concern as, according to data of the Perinatal Information System (SIP, *Sistema Informático Perinatal*), which covers 35% of deliveries in Argentina, only 28.3% of pregnancies were planned and only 29% of pregnant women received prenatal care during the first trimester. (10) In the United States, almost 50% of pregnancies are unintended, (11) and the problem of ACEIs during the first trimester of pregnancy should be considered in women of childbearing age.

By the end of 2002, The Ministry of Health implemented the Remediar Program in Argentina (12) to supply free essential medications, including the ACEI enalapril, to outpatients in the primary care level who live below the poverty line. In addition, a database was constructed with the information from the Remediar Program that allowed, for the first

time, cross comparisons of diagnoses, prescriptions and beneficiaries of the public primary care level in Argentina.

The goal of this investigation was to quantify the prescription of enalapril - an ACEI - provided by the Remediar Program in women of childbearing age as a risk factor for MCMs, and to think about the possible number of MCMs that could be prevented by reducing the exposure to ACEIs in this population.

MATERIAL AND METHODS

The study has two designs: The first design corresponds to an ecological study –observational and descriptive – about the use of medications with cross comparisons of diagnoses and prescriptions in the public primary care level in Argentina. Table 1 summarizes the methodology used for the analysis of the information. The secondary sources of information come from the R-Forms or Remediar Program Forms. The units of analysis are the forms made from March 2005 to February 2006 in almost 6,000 primary health care centers nationwide. The R-Form is the basic instrument of data collection that proves that the drug prescribed during medical consultation, and included in the Remediar kit, was delivered to the patient. The prescription rate was defined as the ratio between prescriptions (R-Forms) and consultations (B-Forms) by population group (adjustment based on results from the survey evaluation program).

The study population is women of childbearing age, aged 15 to 49 years, according to the definition of the WHO. (13) (17) The beneficiaries were unequivocally individualized by means of a verification procedure implemented by the *Sistema de Identificación Nacional Tributario y Social* (SINTyS, National System for Social and Tax Identification) on the ID field in the prescription forms.

We included all forms given to women between 15 and 49 years with: 1. Prescription of enalapril; 2. Diagnosis of HT.

Table 1. Methodology used for the analysis of the information

Source	Content	Unit of analysis	Main indicators
R-Form (Remediar Prescription)	Diagnosis code; – Treatment prescribed; – Patient's basic data (age, gender, etc.)	Universe of 15 million prescriptions from February 2005 to March 2006	– Frequency of <i>diagnosis</i> (prescriptions with diagnosis of diabetes/total prescriptions) – Frequency of <i>treatments prescribed</i> per <i>diagnosis</i> [– Frequency of <i>treatments prescribed</i> per <i>beneficiary</i>
Crossover information of R-Form and SINTyS database	Identification of Remediar beneficiaries	Population who received Remediar medication	– Number of beneficiaries identified by group, age, province, etc.
B-Form (Monthly Medication Consumption and Consultation Records)	– Consumption per medication; – Stock or availability per medication (in moths); – Consultations (total); and – Remediar prescriptions	Total Forms submitted by PHCC, consolidated to present	– <i>Medication prescription rate</i> per 100 consultations; – <i>Availability</i> (months of average use covered by the stocks of medicine left at the each PHCC); – Average consultations and prescriptions per month; – Remediar prescription rate per consultations

Two types of drug utilization studies are applied: Type 1. Diagnosis →prescription studies (medications) and Type 2. Prescription →diagnosis studies. (14)

The second design is an evaluation of the counterfactual approach of the impact that reduced exposure to ACEI might have for the prevention of MCMs in that population. A counterfactual event is a consequence or condition that cannot be observed by human investigation but could have happened. The PICO method is used to build clinical questions about the number of MCMs that could be prevented: (16) Patients or Population, Intervention, Comparison and Outcome. The probable impact was calculated as follows:

- Patients or Population: women aged 15 to 49 years with prescriptions provided by the Remediar Program. Approximately 7.15% of this group gets pregnant each year and has live birth deliveries.
- Intervention: use of ACEI (enalapril) in women of childbearing age estimated from the beneficiaries identified in the Remediar Program database.
- Comparison: the same populations that were not using ACEIs.
- Outcomes: prevention of MCMs is the number of MCMs estimated by the Comparison minus the Intervention.

Only MCMs not related to chromosomal defects or with known genetic syndromes were considered. We used the definition of MCM provided by the Centers for Disease Control and Prevention (CDC) Metropolitan Atlanta Congenital Defects Program. The published risks of MCMs were considered due to lack of national information: (5) it is 2.63% for general pregnancies and increases to 7.12% (2.71 times) when ACEIs are used during the first trimester of pregnancy.

For the evaluation of the counterfactual approach we calculated the 95% confidence intervals to estimate the proportions provided by Cooper et al. (5), using the following formula:

$$\hat{p} - 1.96 \times \sqrt{\hat{p} \times (1 - \hat{p})/n} \leq p \leq \hat{p} + 1.96 \times \sqrt{\hat{p} \times (1 - \hat{p})/n}$$

Confidence intervals are used to estimate the population parameter within the possible value ranges in a specific sample under a given probability, and extrapolating such intervals to other sample implies assuming that both populations have similar characteristics (demographic composition, educational levels, prenatal care, treatment persistence, etc.). However, confidence intervals are only used in this study to make an approximation to a value associated with the outcomes of the use of ACEIs provided by the Remediar Program to women of childbearing age.

As this is an ecological study, it was not evaluated by the Committee on Ethics.

RESULTS

A total of 15,001,041 R-Forms recorded during the year of the study were analyzed. There were 60 prescriptions for each 100 consultations in women of childbearing age. Table 2 shows the descriptive results by beneficiaries, diagnoses and prescriptions in the forms (units of analysis) A total of 2,085,338 women of childbearing age were identified – 21% of the Argentine population of women of childbearing age; – enalapril was prescribed to 113,762 (5.5%) and HT was the most frequent diagnosis. Enalapril is the medication most frequently prescribed in the prescriptions with diagnosis of HT. Figure 1 shows the most frequent prescriptions to women from 15 to 49

years with diagnosis of HT.

The estimated population of women between 15 and 49 years in Argentina by 2006 was 9,796,768 people; there were 696,451 live births during that year, therefore 7.15% of women in that age group have one live birth each year. (17)

If 7.15% of 2,085,338 women aged 15 to 49 years identified by the delivery of medications supplied by the Remediar Program got pregnant and had one live birth in the year, 3,921 children would be born with MCMs, given a risk of MCMs of 2.63%. The risk increases to 7.12% among the 113,762 women identified with a prescription of enalapril: thus, the number of live births with MCMs could be 579 (95% CI, 296 to 863) instead of 214 (95% CI, 199 to 229) in case other medications had been prescribed. Reduction to enalapril exposure during the first trimester could prevent 365 (95% CI, 97 to 634) cases of MCMs/year in the population covered by the Remediar Program.

DISCUSSION

Several aspects should be discussed. There is lack of information about the incidence of MCMs in Argentina; conversely, infant mortality due to MCMs is 3.3‰ and accounts for 22.7% of overall infant mortality. (17, 18) A national registry has to be developed, yet the only data available come from maternity services taking part in the *Estudio Colaborativo Latinoamericano de Malformaciones Congénitas* (ECLAMC).

The original paper about the exposure to ACEIs during the first trimester of pregnancy, and its association with a prevalence of MCMs that was twice that of the general population represents, undoubtedly, a study with valuable information. (5) Using a detailed database, Cooper et al. were the first to demonstrate such an association. The use of medications in women of childbearing age has always concerned the population, physicians and authorities. Many women have unplanned pregnancies, and the number of women who suffer from chronic diseases and receive medications is increasing. The pharmaceutical industry develops medications that are not tested in pregnant women before marketing drugs due to obvious ethical reasons. The information available

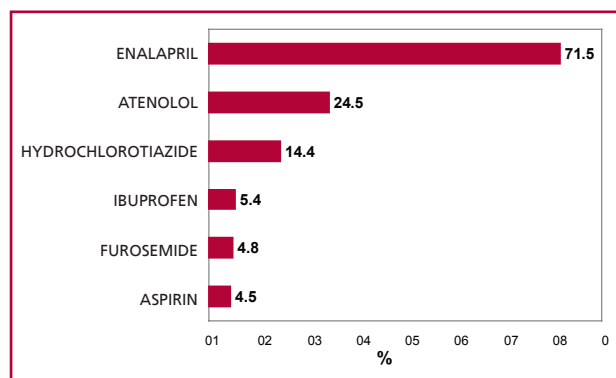


Fig. 1. Frequency of prescription of medications for HT to women aged 15 to 49 years. Source: Prescriptions of the Remediar Program.

about teratogenicity is based on experiments developed in animals and, thus, the clinical interpretation and epidemiological surveillance is difficult, as in this case. Although this study is considered an “exploratory” study (19, 20) it is interesting in the field of human teratology and was incorporated to guidelines (21, 22). The publication of new studies with opposed results does not seem feasible. (19, 20)

The investigation sheds light on the magnitude of the problem of ACEIs prescription in women aged 15 and 49 years in the Argentine primary care level. During the studied period, the risk of having a child with MCMs among the 113,762 women covered by the Remediator Program is 2.71 times greater. The population covered by the program is not representative of the total population of Argentine women of childbearing age; for this reason, these results cannot be extrapolated to the national universe. It would be necessary to develop other type of investigation, as an analytic case-control study, in order to understand the real damage provoked by ACEIs in the first trimester of pregnancy. (23) The use of medications for marketing studies nationwide is estimated by Intercontinental Marketing Services (IMS), which controls retail pharmacy channel sales of medications. (24) The cardiological segment represented 12.1% of total sales for the period 2005-2006. ACEIs (with enalapril representing 89% of all ACEIs) constitute 47.2% of defined daily doses of medications for the treatment of HT. Yet, the limitation of Intercontinental Marketing Services is the lack of information based on the population.

The classification used by the Ministry of Health considers MCMs as causes of mortality unlikely to be reduced. (17) Currently, as most MCMs and CHDs have high survival rates in neonatal and

intensive care units with normal future quality of life, it has been stated that most neonatal and pediatric deaths might be reduced by intermediate and intensive environments providing neonatal care. (25) The Congenital Heart Defects National Program (*Programa Nacional de Cardiopatías Congénitas*, Resolution 107, 2008) was established based on this approach (4), and is supported by the scientific societies. (26) This approach is effective, as it is feasible to perform neonatal cardiac surgeries in Argentina with favorable outcomes, reducing delays in pediatric surgeries. (27) Yet, this approach is expensive, as the Nation will invest more than \$ 580,000,000 for CHDs care. (28) The preventive approach is less expensive; however, it might only be effective if the specific causes were identified. A counterfactual approach states that avoiding exposure to ACEIs in the first trimester of pregnancy might prevent several MCMs per year. Estimating something that has not occurred is controversial; yet this approach is used to evaluate causality in social and health care projects. (15)

Use of ACEIs should be avoided in women of childbearing age due to the possibility of unplanned pregnancies. (21) Women of childbearing age who are sexually active and require ACEIs should receive counseling about the risks of teratogenesis and the benefits to stop taking the medication when the earliest signs of pregnancy appear (29) and switch it to alternate and safer agents. However, an unplanned pregnancy while taking ACEIs increases the risk of malformations and poses other matters, such as what answer should be given to those who would prefer to interrupt pregnancy. (20)

The availability of medications in medical facilities is an intermediate target of health care policies. Provision of supplies should be accompanied by

Indicator	Number	%
R-Forms (prescriptions)		
Total	15,001,041	100
Women aged 15 to 49 years	3,697,761	24.7
Women aged 15 to 49 years with enalapril	188,585	5.1
Beneficiaries identified		
Total	8,119,465	100
Women aged 15 to 49 years	2,085,338	25.7
Women aged 15 to 49 years with enalapril	113,762	5.5
Prescriptions: diagnosis → prescription (*)		
Total diagnoses of HT	1,560,108	10.4
Diagnosis of HT in women aged 15 to 49 years	218,415	1.45
Diagnosis of HT in women aged 15 to 49 years and enalapril prescription	156,166	71.5
Enalapril prescriptions to women ages 15 to 49 years: prescription → diagnosis (*)		
Hypertension		83.0
Diabetes mellitus		5.9
Heart failure/heart diseases		1.5

Table 2. Descriptive results: beneficiaries, diagnoses and prescriptions

Source: Prescriptions of the Remediator Program.

HT: Hypertension

(*) The addition is not 100 as there may more than 1 diagnosis and more than one medication per prescription.

permanent training (medical education), sensitization and information for prescribers and patients, in order to achieve the final target: improvement of quantity and quality of life. The same drug can cure people or produce an illness. Eliminating entrenched practices is more difficult than introducing new ones, as valuable resources are still being used in detrimental practices.

MCMs due to teratogenic medications can be prevented. Yet, potentially teratogenic medications are usually prescribed to women of childbearing age without documentation of contraception. (3) Mothers and their children are unnecessarily exposed to risk due to ignorance. Prescription of ACEIs to women of childbearing age demonstrates that the greater availability of medications is not always the best option.

Family planning, especially in women with chronic diseases, preconception counseling for primary prevention of congenital defects and responsible prescription of medications to women of childbearing age are important.

Study Limitations

The following limitations have been detected:

- Ecological studies are frequently biased. (31)
- Prescription is not equal to use.
- We only analyzed the prescription of medications provided by the Remediar Program.
- Counterfactual scenarios only allow construction of hypothesis.
- The study by Cooper et al (5) is exploratory (19, 32, 33) and based on a different population. More evidence is needed.

CONCLUSIONS

Prescription of ACEIs to women of childbearing age is frequent and may not be considered safe. A significant number of cases of MCMs would be prevented avoiding the prescription and use of ACEIs in this population. More evidence is needed to evaluate this risk.

RESUMEN

Prescripción de enalapril a la mujer fértil como factor de riesgo de malformaciones congénitas en el primer nivel de atención pública de la Argentina

Introducción

El uso de inhibidores de la enzima convertidora de la angiotensina II (IECA) en el primer trimestre del embarazo se asocia con un incremento de 2,71 veces del riesgo de malformaciones congénitas mayores (MCM), lo cual genera preocupación debido a que los IECA constituyen uno de los medicamentos prescritos con más frecuencia.

Objetivo

Cuantificar la prescripción de enalapril –un IECA– provisto por el Programa Remediar a mujeres en edad fértil y reflexionar acerca del posible número de MCM que podrían prevenirse.

Material y métodos

El estudio consta de dos diseños: 1. Estudio ecológico: cruce de diagnósticos, prescripciones, beneficiarios de las recetas del Programa Remediar (fuentes secundarias). Población objetivo: mujeres de 15 a 49 años atendidas en 6 mil centros de salud de la Argentina desde 2005 hasta 2006, con diagnóstico de hipertensión y/o prescripción de enalapril. 2. Evaluación sobre un enfoque contrafáctico del impacto que podría tener la reducción de la exposición a IECA en esa población.

Resultados

Se analizaron 15.001.041 Formularios R, universo de recetas grabadas en el año estudiado. Se identificaron 2.085.338 mujeres en edad fértil y se prescribió enalapril al 5,5% de ellas; esto elevaría la cantidad de MCM de 214 (IC 95% 199-229), si se hubieran prescrito otros medicamentos, a 579 con el uso de enalapril (IC 95% 296-863), de modo que con la reducción de la exposición podrían prevenirse alrededor de 365 (IC 95% 97-634) casos/año de MCM en la población cubierta por Remediar.

Conclusiones

La prescripción de IECA a mujeres en edad fértil es frecuente. En esta población se prevendrían numerosos casos de MCM si se evitaran la prescripción y el uso de IECA. Se requiere mayor evidencia para evaluar el riesgo descripto.

Palabras clave > Enalapril - Anomalías congénitas - Utilización de medicamentos - Prevención

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