

## **R03 – Aerosol-type Adrenergic Agents**

### **R03AC – Selective agonists of 2-adrenergic receptors**

Sympathomimetics affecting 2-receptors may inhibit uterine muscle, and it is therefore employed in the treatment of pre-term birth.

#### **Prospective cohort studies with internal controls**

- Schatz et al (1997): a cohort study of 824 newborns to mothers suffering from asthma, and a control group of 678 newborns to non-asthmatic mothers were monitored. Interviews were based on drugs exposure of both groups before the 28<sup>th</sup> week of gestation. Data were analyzed by groups of drugs used in the treatment of maternal asthma and the offspring exposed to a specific drug compared with offspring not exposed to that drug but possibly exposed to another antiasthmatic. 488 newborns were exposed to one or more beta-agonist. The following inhalants had been administered: 309 metaproterenol, 316 terbutaline, 129 albuterol, and 82 isoetharine; 69 more were systemic medicaments: 76 terbutaline; 60 ephedrine; 31 epinephrine; 20 susphirine; 10 others. 1,000 controls were not exposed. 21 exposed newborns had congenital anomalies vs. 56 out of the controls. RR = 0.8 (CI 95%: 0.5-1.3).

#### **Salbutamol (Albuterol) – R03AC02 – R03AK04 – R03CC02 – R02CK**

Patented in 1967.

#### **Retrospective cohort studies with internal controls**

- Rosa (1993), Michigan, MSS: 1,090 first trimester exposures, 48 newborns with major defects, 43 expected. RR = 1.1 (CI 95%: 0.8-1.5).

#### **Case-control studies nested in the prospective cohort of all newborns, specific**

- Kallen and Otterblad Olausson (2003), Swedish MBR: 5,015 cases of newborns with cardiovascular defects, 29 of which exposed to salbutamol; 577,730 controls, 3,475 of which were exposed. OR of cardiopathy for first trimester exposure = 0.9 (CI 95%: 0.6-1.4).

**Feto-neonatal effects:** Systemic treatment can be causative of maternal hypotension (Korda et al 1974, Ng and Sen 1974, Hastwell et al 1978, Wager et al 1982), maternal and fetal transitory hyperglycemia (Lunell et al 1977, Thomas et al 1977, Hastwell et al 1978, Wager et al 1981, Procianoy and Pinheiro 1982), fetal and maternal tachycardia (Liggins and Vaughan 1973, Korda et al 1974, Hastwell 1975, Eggers et al 1979, Wager et al 1982, Baker and Flanagan 1977), intense cardiac decompensation, pulmonary edema (Whitehead et al 1980, Pode-Wilson 1980, Fogarty 1980, Davies 1980, Crowley 1980, Robertson and Davies 1980), and maternal death (Milliez et al 1980). No adverse effects were uncovered in systemic exposures after the first trimester (Lind et al 1980, Addis 1981, Edmonds and Lechtworth 1982, Gummerus and Halonen 1987, Rayburn et al 1994).

#### **Terbutaline – R03AC03**

Patented in 1967.

#### **Retrospective cohort studies with internal controls**

- Rosa (1993), Michigan MSS: of 149 first trimester exposures, 7 newborns had major defects, 6 expected. RR = 1.2 (CI 95%: 0.5-2.4).

#### **Case-control studies nested in the prospective cohort of all newborns, specific**

- Kallen and Otterblad Olausson (2003), Swedish MBR: 5,015 cases of newborns with cardiovascular defects, 104 of which exposed to terbutaline; 577,730 controls, 10,717 of which exposed. OR for cardiopathy in first trimester exposures = 1.1 (CI 95%: 0.9-1.4).

Feto-neonatal effects: Systemic exposure can be causative of hypotension, maternal and neonatal hypoglycemia, maternal and fetal tachycardia, respiratory distress, and paralytic ileum (Briggs et al 2002).

#### **Salmeterol – R03AC12 – R03AK06**

It is available in Italy since 1997.

#### **Prospective cohort studies without controls**

- Wilton et al (1988): 1 newborn with congenital anomaly (Aarskog syndrome) out of 47 newborns exposed in the first trimester.

#### **Case-control studies, specific, nested in the prospective cohort of all newborns**

- Kallen and Otterblad Olausson (2003), Swedish MBR: 5,015 cases of newborns with cardiovascular defects, 15 of which exposed to salmeterol; 577,730 controls, 1,152 of which exposed. OR for cardiopathy in first trimester exposures = 1.5 (CI 95%: 0.9-2.5).

#### **Formoterol – R03AC13**

Patented in 1973

We have been unable to locate references on possible human reproductive effects of this agent.

#### **Studies on laboratory animals**

- Stato et al (1984): nonteratogenic in rats (60 mg per os) and rabbits (600 mg per os).

#### **Clenbuterol – R03AC14 – R03CC13**

Patented in 1967.

We have been unable to locate references on possible human reproductive effects of this agent.

#### **Studies on laboratory animals**

- Matsuzawa et al (1984): nonteratogenic in rats and rabbits (up to 50 mg/kg).

**Feto-neonatal effects:** A 7% increase of fetal cardiac frequency has been noticed

(Wladimiroff and Roodenburg 1982).

### **Reproterol – R03AC15**

It is available in Italy since 1987.

We have been unable to locate references on possible human reproductive effects of this agent.

#### **Studies on laboratory animals**

- Habersang et al (1977): nonteratogenic in rats (320 mg/kg per os and 120 mg/kg intravenous) and in rabbits (180 mg/kg per os and 30 mg/kg intravenous)

### **Procaterol – R03AC16 – R03CC08**

It is available in Italy since 1984.

We have been unable to locate references on possible human reproductive effects of this agent.

#### **Studies on laboratory animals**

- Minami et al (1979): nonteratogenic in rats (up to 250 mg/mg/kg per os from day 7 to 17), but delayed ossification and dilatation of renal pelvis at the highest dosage.
- Tamagawa et al (1979): nonteratogenic in rabbits (500 mg/kg per os from day 6 to 18).

### **Fenoterol – R03AK03 – R03CC04**

Patented in 1967

We have been unable to locate references on possible human reproductive effects of this agent.

#### **Studies on laboratory animals**

- Nishimura et al (1981): nonteratogenic in rats (up to 25 mg/kg/day) and rabbits (100 mg/kg/day).

**Feto-neonatal conclusions:** Used in case of threatened pre-birth it has not caused maternal or fetonatal adverse effects. (Onnis et al 1983).

**R03AC Class Conclusions:** Some substances belonging to this class have been thoroughly and specifically studied, but we have been unable to find enough data relevant to the use of other substances in human pregnancy. Altogether, a reproductive risk increase is not likely, in consideration of the available studies, the type of administration, the lack of anomalies over the long period of commercialization and of teratogenic activity in laboratory animals (records provided by manufacturer for registration, not available in database). ADEC considers salbutamol, terbutaline and fenoterol drugs of choice in pregnancy.

## **R03BA – Glucocorticoids**

These are steroids synthesized by adrenal gland. Only 10-20% of inhaled dose reaches lungs (Glaxo 1980). Dosage employed for inhalants are one sixth lower than oral dosages (Brompton Hospital 1974). Glucocorticoids are mainly employed for their antiinflammatory and immunosuppressant activity.

### **Case-controls studies, specific, nested in the prospective cohort of all newborns**

- Kallen and Otterblad Olausson (2003), Swedish MBR: 5,015 cases of newborns with cardiovascular defects, 66 of whom exposed to inhalant corticosteroids; 577,730 controls, 7,404 of whom exposed. OR for cardiopathy in first trimester exposure = 1.0 (CI 95%: 0.8-1.3). 31 exposures to rhinal corticosteroids; 2,872 exposures out of 577,730 controls, OR = 1.2 (CI 95%: 0.9-1.8).

## **Beclomethasone – R03BA01**

Patented in 1967.

### **Cohort studies without controls**

- Greenberger and Patterson (1983): Of 43 exposures to inhalants in the first trimester of pregnancy, 42 healthy newborns, and one congenital cardiopathy (diabetic mother).
- Fitzsimons et al (1986): 56 healthy newborns exposed in the first trimester of pregnancy.

### **Retrospective cohort studies with internal controls**

- Rosa (1993), Michigan MSS: Of 395 first trimester exposures, 16 newborns had major defects, 16 expected. RR = 1.0 (CI 95%: 0.6-1.6).

### **Prospective cohort studies with internal controls**

- Schatz et al (1997): 824 newborns to mothers suffering from asthma in the studied cohort, and 678 newborns to non asthmatic mothers in the control cohort; for both cohorts interviews were based on drugs exposures prior to the 28<sup>th</sup> week of gestation. Data were analyzed divided per each group of drugs employed in the treatment of maternal asthma, and the offspring exposed to one drug was compared with offspring not exposed to that very drug, but possibly to other antiasthmatic medicaments. 204 newborns were exposed in the first trimester to rhinal, inhalant and oral corticosteroids, mostly Beclomethasone. There were 1,295 nonexposed controls; 14 exposed newborns had congenital anomalies, vs. 63 out of the controls. RR = 1.4 (CI 95%: 0.8-2.5)

## **Budesonide – A07EA06 – D07AC09 – R01AD05 – R03BA02**

Patented in 1973.

### **Cohort studies without controls**

- Astra (1999), manufacturer: Of 15 newborns exposed in unspecified periods, 13 healthy newborns and 2 with congenital anomalies.

### **Prospective cohort studies with external controls**

- Kallen et al (1999), Swedish MBR: 2,104 exposures to inhalant budesonide with an incidence of congenital anomalies of 2.8% (41 major and 35 minor) similar to the incidence observed in the rest of the population (3.5%). A specific analysis for oral schisis

(4 cases vs. 3.3 expected) does not suggest an association with such defects.

### **Case-control studies, specific, nested in the prospective cohort of all newborns**

- Kallen and Otterblad Olausson (2003), Swedish MBR: 5,015 cases of newborns with cardiovascular defects, 62 of whom exposed to budesonide; 577,730 controls, 6,557 of whom exposed. AOR for cardiopathies = 1.1 (CI 95%: 0.9-1.4). The analysis per subgroups of rhinal exposures suggested an association with slight cardiac defects (a further subcategory had poor biologic interest): OR = 1.6 (CI 95%: 1.0-2.5). This result may be due to multiple-matching bias and to a posteriori analysis of specific subgroups.

**Feto-neonatal effects:** No differences in gestational age, neonatal weight, stillbirth, twins, increase in caesarian birth vs. nonexposed (Norjavaara and de Verdier 2003).

### **Flunisolide – R03BA03**

It is available in Italy since 1984

We have been unable to locate references on possible human reproductive effects of this agent.

### **Studies on laboratory animals**

- Itabashi et al (1982): nonteratogenic in rats at 50 g/kg per os; increased in umbilical hernia, anasarca and cleft lip at 100 g/kg. Nonteratogenic in mice at 0.04 mg/kg; cleft lip increase at 0.2 mg/kg.

### **Fluticasone – R03BA05**

This agent has a high catabolism of first hepatic crossing, therefore possibly having a poor systemic bioavailability (Holiday et al 1994). It is available in Italy since 1996.

We have been unable to locate references on possible human reproductive effects of this agent.

### **Studies on laboratory animals**

- Shimpo et al (1992 a, b): increase in omphalocele and skeletal changes in rats (100 subcutaneous mg/kg)
- Rawlings et al (1992): pulmonary alterations and of liver lobules in rabbits (4 mg/kg).

**R03BA Class Conclusions:** We do have some vast studies on some of the agents in this class, and they do not suggest a risk increase in congenital anomalies. The hypothesis raised by a Swedish study, concerning a slight risk increase of cardiopathy following inhalant budesonide, deserves a deeper survey although the connection might be biased by multiple matching. ADEC considers inhalant budesonide a drug of choice in pregnancy.

### **R03BB – Anticholinergic medicaments**

### **Ipratropium bromide – R01AX03 – R03BB01**

This is a quaternary ammonic compound. Patented in 1972.

### **Case report**

- Gilchrist et al (1991): 1 healthy newborn exposed on 12<sup>th</sup> and 13<sup>th</sup> week.

### **Retrospective cohort studies with internal controls**

- Rosa (1993), Michigan MSS: 37 first trimester exposures, 1 newborn with renal obstruction.

### **Bromide Oxytropium – R03BB02**

Patented in 1966.

We have been unable to locate references on possible human reproductive effects of this agent.

### **Studies on laboratory animals**

- Savary and Glomot (1989): nonteratogenic in rats (600 mg/kg/day) and rabbits (200 mg/kg/day).

**R03BB Class Conclusion:** There are few studies and this fact contrasts with the probably very large use of these agents, also in pregnancy, particularly in the case of their father, Ipratropium bromide. In case of exposure the following arguments should be considered for advice: the lack of reported increased anomalies over the long period of commercialization, and of teratogenic activity in laboratory animals (records provided by manufacturer for registration, not available in database). ADEC considers Ipratropium bromide a drug of choice in pregnancy.

### **R03BC – Antiallergic agents**

#### **Nedocromil R03BC03**

This is pharmacologically totally similar to chromolin (Wasserman 1993, Brogden and Sorkin 1995). Systemic absorption of 5% of aerosol administered dose and less than 4% in case of eye drops. It is available in Italy since 1989.

### **Case report**

- Carrasc and Sepulveda (1988): Of 3 exposures in the early 8 weeks, 1 miscarriage and 2 healthy newborns.

### **Prospective cohort studies without controls**

- Wilton et al (1998): Of 32 first trimester exposures, 22 healthy newborns, 1 miscarriage, 8 VIP, and 1 newborn with congenital cardiopathy also exposed to aminofiline, salbutamol, and corticosteroids.

### **Prospective cohort studies with internal controls**

- Schatz et al (1997): cohort study of 824 newborns to mothers suffering from asthma, and a control cohort of 678 newborns to non-asthmatic mothers; interviews for both cohorts

were based on drugs exposures prior to the 28<sup>th</sup> week of gestation. Data were analyzed divided per each group of drugs employed in the treatment of maternal asthma, and the offspring exposed to one drug was compared with offspring not exposed to that very drug, but possibly exposed to other antiasthmatic medicament. 151 were exposed in the first trimester to inhalant, rhinal and ophthalmic cromolyn. Nonexposed controls: 1.348. 9 exposures for congenital anomalies, vs. 67 out of controls. RR = 1.2 (CI 95%: 0.6-2.4).

**Conclusions:** A vast study on cromolyn suggests no risk increase in congenital anomalies.

### **R03C – Adrenergic agents for systemic use**

These are playing a main role as bronchodilators in the treatment of asthma, acting in lungs as receptors stimulants, thus relaxing bronchial smooth muscles. Inhalant administration brings about a reduced systemic concentration, but only 10% of inhaled dose reaches lungs, while the rest is swallowed and, on principle, absorbed (Newhouse and Dolovich 1986).

### **R03CA – Antagonists of Alfa and Beta-adrenergic receptors**

#### **Ephedrine – R01AB05 – R03CA02**

Patented in 1962.

#### **Case report**

- Matsuoka et al (1985): 1 fetus with congenital cardiopathy exposed over the first period of pregnancy to a medicament containing ephedrine, theophylline and phenobarbital.
- Gilbert-Barness and Drut (2000): 1 newborn with reduced limbs exposed to a medicament containing ephedrine, theophylline and phenobarbital.

#### **Prospective cohort studies with internal controls**

- Heinonen et al (1977), CPP: 17 newborns with congenital anomalies, out of 373 exposures in the first 16 weeks. ARR = 1.0 (CI 95%: 0.6-1.6).

**Conclusions:** According to the few studies on the use of ephedrine in human pregnancy, a risk increase in congenital anomalies is not likely. ADEC considers it a drug of choice in pregnancy. Two recent studies on gastroschisis (Werler et al 1992, Torfs 1996) suggested the possibility of a low risk increase in this particular rare defect in association with pseudo-ephedrine (ephedrine stereoisomer). This is a hypothesis to be further considered.

### **R03CB – Non-selective agonists of beta-adrenergic receptors**

#### **Orciprenaline (Metaproterenol) – R03CB03**

This is a resorcinol derivative. Patented in 1960.

#### **Retrospective cohort studies with internal controls**

- Rosa (1993), Michigan MSS: Of 361 first trimester exposures, 17 newborns had major defects, 15 expected. RR = 1.1 (CI 95%: 0.7-1.8).

**Feto-neonatal effects:** This agent is used in the treatment of threatened pre-birth and in uterine hypertonia during labor, with no adverse effects in the fetus, except for sinus tachycardia (Working Group on Asthma and Pregnancy 1993).

**Conclusions:** The sole study we know about does not suggest risk increase in birth defects. A lack of anomalies over the long period of commercialization and the lack of teratogenic activity in laboratory animals should be considered. ADEC reckons orciprenaline a drug of choice in pregnancy.

## **R03D – More systemic drugs for obstructive syndrome of the respiratory tract**

### **R03DA – Xanthine derivatives**

Methylxanthines like theophylline, caffeine, and theobromine are natural alkaloids found in tea, cocoa, chocolate, coffee, and in nuts of *Kola acuminata*, used in drinks. They release smooth bronchial muscles.

### **Diprophylline – R03DA01**

This is a synonym of diphyllyne and it is pretty similar to theophylline. Patented in 1951.

### **Theophylline – R03DA04**

Patented in 1949.

## **Case report**

- Halbrecht et al (1973): 1 stillbirth with triploidy exposed throughout pregnancy to high doses of a medicament containing theophylline, ephedrine, phenobarbital and diphenhydramine.
- Matsuoka et al (1985): 1 fetus with congenital cardiopathy exposed over the first period of pregnancy to a medicament containing theophylline, ephedrine and phenobarbital.
- Park et al (1990): 3 newborns with congenital cardiopathy exposed throughout pregnancy.

## **Retrospective cohort studies with internal controls**

- Rosa (1993), Michigan MSS: Of 1,240 first trimester exposures, 68 newborns had major defects, 53 expected. RR = 1.3 (CI 95%: 0.9-1.6).

## **Prospective cohort studies with internal controls**

- Heinonen et al (1977), CPP: Of 117 exposures in the first 16 weeks, 5 newborns had congenital anomalies. ARR = 0.9 (CI 95%: 0.4-2.2).
- Stenius Aarniala et al (1995): 3 congenital anomalies out of 121 first trimester exposures, vs. 4 out of 91 newborns exposed only in the 2<sup>nd</sup> and 3<sup>rd</sup> trimester (RR = 0.6; CI 95%: 0.1-2.5) or vs. 3 out of 237 infants born to non-asthmatic mothers (RR = 2.0; CI 95%: 0.4-9.6).
- Schatz et al (1997): A studied cohort of 824 newborns to mothers suffering from asthma, and a control cohort of 678 infants born to non-asthmatic mothers. Interviews were

based on drugs exposure of both groups before the 28<sup>th</sup> week of gestation. Data were analyzed by groups of drugs used in the treatment of maternal asthma and the offspring exposed to a specific drug compared with offspring not exposed to that drug but possibly exposed to another antiasthmatic. 292 first trimester exposures to theophylline; 1,208 non-exposed controls. 13 exposed newborns had congenital anomalies, vs. 64 out of the controls. RR = 0.8 (CI 95%: 0.5-1.5).

**Feto-neonatal effects:** high administered doses prolonged over the late period of pregnancy caused transitory tachycardia, irritability and vomiting (Yeh and Pildes 1977, Arwood et al 1979), beside apparent withdrawal symptoms (Horowitz et al 1982).

### **Aminophylline – R03DA05**

Patented in 1949.

#### **Retrospective cohort studies with internal controls**

- Rosa (1993), Michigan MSS: Of 36 first trimester exposures, 1 newborn with major defects, 2 expected. RR = 0.5 (CI 95%: 0.0-2.8).

#### **Prospective cohort studies with internal controls**

- Heinonen et al (1977) CPP: Of 76 exposures in the first 16 weeks, 4 newborns with congenital anomalies. ARR = 1.2 (CI 95%: 0.5-3.0).

#### **Case-control studies, specific**

- Medveczky et al (2004), Hungarian CCSCA: 1,202 newborns with DNT, 21 of whom exposed in the 2<sup>nd</sup> month of gestation (critical period for DNT); 38,151 healthy controls, 1,318 of whom exposed with OR = 0.5 (CI 95%: 0.1-2.1), and 22,475 controls with other congenital anomalies, 185 of whom exposed with OR = 0.4 (CI 95%: 0.1-1.7).

**Feto-neonatal effects:** high administered doses prolonged over the late period of pregnancy caused transitory tachycardia, irritability and vomiting (Yeh and Pildes, Arwood et al (1979).

### **Bamifilline – R03DA08**

Patented in 1961.

We have been unable to locate references on possible human reproductive effects of this agent.

#### **Studies on laboratory animals**

- Georges and Deneff (1968): nonteratogenic in rats (1,000 mg/kg/day per os on days 10 to 12).

### **Doxofilline – R03DA11**

It is available in Italy since 1984.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

**R03DA Class Conclusions:** There are no findings of risk increase in birth defects in the studies relevant to theophylline and aminophylline. Clinical experience over the long period of commercialization of progenitor drugs appears to be much larger than what signaled in the available studies. Different authors (Greenberger and Patterson 1979, Weinstein et al 1979, Hernandez et al 1980, Turner et al 1980, Berkowitz et al 1986) and ADEC consider aminophylline and theophylline drugs of choice in the treatment of asthma during pregnancy.

### **R03DC – Antagonists of leukotrienic receptors**

Leukotrienes produce, besides other outcomes, the contraction of smooth muscles, edema of respiratory tract, and cellular activities; besides, they aid eosinophil granulocytes enter lungs. Antileukotrienes foster leukotrienic receptors LTC<sub>4</sub>, LTD<sub>4</sub> and LTE<sub>4</sub> in a competitive and selective way.

#### **Zafirlukast – R03CC01**

It is available in Italy since 1998.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

#### **Montelukast – R03DC03**

It is available in Italy since 1998.

### **Cohort studies without controls**

- Merck (2000): out of a total of 18 prospective exposures, 14 occurred in the first trimester, 1 in the 2<sup>nd</sup>, 1 in the 3<sup>rd</sup> and 2 in unknown period. None of the newborns had congenital anomalies. Out of 6 retrospective cases there were 3 miscarriages, 3 healthy newborns, 1 maternal death for severe asthma. 38 first trimester different clinical trials were recorded. The outcome was unknown in 3 cases; 9 miscarriages, 9 VIP, 1 fetal death for preeclampsia, and 16 healthy newborns were reported.

**R03DC Class Conclusions:** We have been unable to find specific studies relevant to the use of antagonists of leukotrienic receptors in human pregnancy, considering that they are being marketed only recently. The sole possible evaluation is therefore based on laboratory animals' studies that have not uncovered any teratogenic activity (records provided by manufacturer for registration, not available in database).

### **R03DX – More drugs**

#### **Fenspiride – R03DX03**

Patented in 1968.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

**Conclusions:** There are no specific studies relevant to the use of this drug in human

pregnancy. In case of exposure the absence of teratogenic activity is the only possible argument (records provided by manufacturer for registration, not available in database).

## **R05CA – Expectorants**

### **Guaifenesin – R05A03**

Patented in 1948.

#### **Retrospective cohort studies with internal controls**

- Aselton et al (1985), Seattle GHC: 241 first trimester exposures. 5 newborns with non-specified congenital anomalies (2.1%). Of 85 exposures to guaifenesin + codeine in the first trimester, 2 newborns with non-specified congenital anomalies. RR for exposure to guaifenesin = 1.3 (CI 95%: 0.6-2.8).
- Rosa (1993), Michigan MSS: Of 141 first trimester exposures, 9 newborns had major defects, 6 expected. RR: 1.5 (CI 95%: 0.7-2.8).

#### **Prospective cohort studies with internal controls**

- Heinonen et al (1997), CPP: of 197 exposures in the first 16 weeks, 6 newborns with congenital anomalies. ARR = 0.7 (CI 95%: 0.3-1.5).

#### **Case-control studies, specific**

- Shaw et al (1998), California BDMP: 538 cases of newborns with neural tube defect; 539 healthy controls. 12 exposures vs. 6 controls. OR = 2.0 (CI 95% : 0.8-5.3).

**Conclusions:** No evidence has been found of an association between guaifenesin and reproductive risk increase, which is not likely since no anomalies were recorded over the long period of commercialization and there is a lack of teratogenic activity in laboratory animals (records provided by manufacturer, not available in database). ADEC considers it a drug of choice in pregnancy.

### **Guaiacol sulfonate – R05CA09**

It is available in Italy since 1981.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

**Conclusions:** No specific studies have been found in literature, relevant to the use of guaiacol sulfonate in human pregnancy. A reproductive risk increased is not likely, in consideration of the lack of reported anomalies over the long period of commercialization and the lack of teratogenic activity in laboratory animals (records provided by manufacturer for registration, not available in database).

## **R05CB – Mucolytics**

These are medicaments with mucolytic-fluidifying activity on the mucous secretion: they break disulfide bonds of mucous glucoproteins; they also prevent polymerization of mucus, consequently decreasing viscosity.

### **Acetylcysteine – R05CB01 – S01X08 – V03AB23**

Patented in 1963.

#### **Cohort studies without controls**

- Riggs et al (1989), Rocky Mountain Poison and Drug Center: 24 women treated with N-acetylcysteine as antidote for paracetamol overdose at different stages of pregnancy. 14 healthy newborns, 5 VIP, 4 miscarriages, 1 stillbirth, 1 maternal death. The earlier N-acetylcysteine is administered (within 10 hours) the better is the outcome.

### **Bromexine – R05CB02**

Patented in 1976.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

### **Carbocysteine – R05CB03**

Patented in 1976.

We have been unable to locate references on possible human reproductive effects of this agent.

#### **Studies on laboratory animals**

- Ito et al (1977 a, b): nonteratogenic in rats (500 mg/kg/day) and rabbits (250 mg/kg/day).
- Kawataba and Sugimoto (1979): nonteratogenic in rats.

### **Mesna – R05CB05**

Patented in 1971.

We have been unable to locate references on possible human reproductive effects of this agent.

#### **Studies on laboratory animals**

- Komai et al (1990): nonteratogenic in rats at 400 intravenous mg/kg on days 7 to 17, while at 800 mg/kg lumbar ribs were uncovered.

### **Ambroxol – 505CB06**

Patented in 1967.

We have been unable to locate references on possible human reproductive effects of this agent

during the first trimester of pregnancy of pregnancy.

### **Studies on laboratory animals**

- Iida et al (1981): nonteratogenic in rats (up to 300 mg/kg) and in rabbits (up to 200 mg/kg)
- Matsuzawa et al (1981): nonteratogenic in rats (500 mg/kg per os on days 7 and 17 to 20).

**Feto-neonatal effects:** ambroxol can speed up fetal maturation of granular pneumocytes and prevent hyaline membrane disease if used for at least 5 days prior to delivery and anyway after 32 weeks of gestation (Wauer et al 1982, Kimya et al 1995, Laoag-Fernandez et al 2000); it is as good as betamethasone (Vytiska-Binstorfer et al 1986, Salzer et al 1986, Heytmanek et al 1990), better than betamethasone (Lucerti et al 1987, Wolff et al 1987), inefficacious (Bomba-Opon et al 2000).

### **Sobrerol – R05CB07**

Patented in 1957.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

### **Tiopronin – R05CB12**

Patented in 1962.

We have been unable to locate references on possible human reproductive effects of this agent.

Studies on laboratory animals

- Fujimoto et al (1979): nonteratogenic in mice.

### **Neltenexine – R05CB14**

It is available in Italy since 1993.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

### **Erdosteine – R05CB15**

It is available in Italy since 2000.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

### **Carbolidine – R05CB49**

It is available in Italy since 1990.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

#### **Mediacisteine (N, S-discetil-cisteinate methile) – R05CB 49**

It is available in Italy since 1997.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

#### **Taurosteine – R05CB49**

It is available in Italy since 1998.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

#### **Telmesteine – R05CB49**

It is available in Italy since 1991.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

**R05CB Class Conclusions:** There are no specific studies relevant to the use in human pregnancy of agents belonging to this therapeutic class. In case of exposure the following arguments can be used in advice: the nature of these agents, the lack of reported anomalies over the long period of commercialization (at least for some of them), and the lack of teratogenic activity in laboratory animals. ADEC considers bromhexine a drug of choice in pregnancy.

#### **R05D – Cough Sedatives**

#### **R05DA – Opium Alkaloids and its derivatives**

#### **Dextromethorphan – R05DA09**

This is a codeine isomer and levorphanol derivative. Patented in 1957.

#### **Case report**

- Robinson and Tross (1984): 4 exposed newborns with defects due to cloacal membrane agenesis (lack of external genitals, anal, urinary and genital orifice, and persistent cloaca).

#### **Retrospective cohort studies with internal controls**

- Aselton et al (1985), Seattle GHC: 59 first trimester exposures, 1 newborn with nonspecific congenital anomaly, RR = 1.1 (CI 95%: 0.2-7.4).

### **Prospective cohort studies with internal controls**

- Heinonen et al (1977), CPP: 300 exposures in the early 16 weeks, 17 newborns with congenital anomalies: ARR = 1.2 (CI 95%: 0.7-1.9).
- Einarson et al (2001), TIS Motherisk: 184 exposures (128 in the first trimester), as many controls. 172 live births, 10 miscarriages (5.4%), 1 VIP and 1 stillbirth out of the exposures. 174 live births, 8 miscarriages (4.3%), and 2 VIP out of the controls. 3 newborns exposed in the first trimester had major birth defects, out of which 1 chromosomal anomaly, and 7 had minor defects. 5 controls had major birth defects, out of which 1 chromosomal anomaly, and 8 had minor defects. RR for any type of congenital anomaly = 1.0 (CI 95%:0.5-2.3), for major congenital anomalies = 0.8 (CI 95%: 0.2-3.3).

### **Case-control studies**

- Martinez-Frias and Rodriguez-Pinilla (2001), ECEMC: 27,864 cases with congenital anomalies. 70 exposures vs. 48 controls, OR = 1.4 (CI 95%: 0.97-2.1). Analysis for specific defects: for DTN AOR = 0.7 (CI 95% : 0.1-4.9); for hydrocephaly AOR = 3.4 (CI 95%: 0.4-30.4); for congenital cardiopathies AOR = 0.9 (CI 95%: 0.1-6.6); for facial schisis AOR = 4.7 (CI 95%: 0.6-40.2).

**Conclusions:** According to the available studies there is no risk increase for birth defects. ADEC, Working Group on Asthma and Pregnancy (1994) and Motherisk Program (Koren 2001) consider it a drug of choice in pregnancy.

### **Dimemorfan – R05DA11**

It is available in Italy since 1987.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

### **Codeine – R05DA20 – R05FA02 – N02BE51**

Patented in 1912.

### **Retrospective cohort studies with internal controls**

- Aselton et al (1985), Seattle GHC: of 347 first trimester exposures to paracetamol in association with codeine, 3 newborns had non-specified congenital anomalies (0.9%). Of 85 first trimester exposures to guaifenesin in association with codeine, 2 newborns had non-specified congenital anomalies. Of 144 first trimester exposures to terpin in association with codeine, 1 single newborn had non-specified congenital anomalies; RR for exposures to codeine = 0.7 (CI 95%: 0.3-1.5).

### **Prospective cohort studies with internal controls**

- Heinonen et al (1977), CPP: of 563 exposures in the first 16 weeks, 32 newborns with congenital anomalies. ARR = 1.2 (CI 95%: 0.8-1.6).

### **Case-control studies, nonspecific**

- Nelson and Forfar (1971): 458 cases of newborns with congenital anomalies (175 major

and 283 minor defects); 911 healthy controls. 10 exposures vs. 16 controls. OR = 1.3 (CI 95%: 0.5-2.9).

- Bracken and Holford (1981): 1,370 cases of newborns with different congenital anomalies; 2,968 healthy controls. 12 newborns with congenital anomalies out of the first trimester exposures, vs. 7 controls (OR = 3.7 (CI 95%: 1.4-10.5)). The result is attributable to memory bias and interview, as shown in a following study on cardiopathies (see Bracken 1986).

### **Case-control studies, specific**

- Bracken (1986): 330 cases of newborns with cardiovascular defects; 3,002 healthy controls. OR for first trimester exposures = 2.4 (CI 95%: 1.1-5.2). Controls matched with other congenital anomalies: OR = 1.3 (CI 95%: 0.7-3.9). The result clearly shows an exposure-ascertainment bias.
- Rothman et al (1979): 390 cases of newborns with cardiovascular anomalies; 1,254 healthy controls. 5 newborns out of first trimester exposures had congenital anomalies, vs. 4 out of the controls (OR = 2.0; CI 90%: 1.3-1.3).
- Zieler and Rothman (1985): 298 cases of newborns with cardiac defects; 738 healthy controls. 14 newborns with congenital anomalies out of the first trimester exposures cases, vs. 18 out of the controls (OR = 2.0; CI 90%: 1.1-3.6). The analysis for specific defects revealed that the association might be attributable to the double exit of the right ventricle (2 cases) AOR = 5 (CI 90%: 1.2-21.7).
- Shaw et al (1992): 141 cases of newborns with isolated different congenital anomalies; 176 healthy controls. OR for exposure to codeine = 0.7 (CI 95%: 0.2-2.4).
- Shaw et al (1998): 538 cases of newborns with neural tube; 539 healthy newborns. 8 exposed cases vs. 9 controls: OR = 0.9 (CI 95%: 0.4-2.2).

### **Retrospective cohort studies with internal controls**

- Rosa (1993), Michigan MSS: 7,640 first trimester exposures, 375 newborns with major defects, 325 expected. RR = 1.1 (CI 95%: 0.8-1.4).

**Feto-neonatal effects:** withdrawal symptoms and respiratory distress in exposures during the latest period of pregnancy (Van Leeuwen et al 1965, Mangurten and Benawra 1980, Khan and Chang 1997).

**Conclusions:** None of the studies on first trimester exposures to codeine have uncovered a reproductive risk-increase. ADEC and Motherisk Program (Koren 2001), in fact, consider it drug of choice in pregnancy. An association with congenital cardiopathies is likely, particularly for some specific cardiopathies, and the critical analysis of the studies has not thoroughly denied it. An ascertainment bias on cardiopathies is suggested by Kallen and Otterblad Olausson, but not proved, since general "cough drugs" have been taken in consideration (AOR = 1.1; CI 95%: 0.8-1.7). The question deserves future investigation; precautionary attitude concerning prescriptions is meanwhile recommended. In case of exposure there is almost no risk.

### **Dihydrocodeine – R05DA49**

Patented in 1955.

See Codeine

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

## **R05DB – More cough sedatives**

### **Clobutinol – R05DB03**

Patented in 1964.

We have been unable to locate references on possible human reproductive effects of this agent.

#### **Studies on laboratory animals**

- Kataoka et al (1970): no fetal or post-natal adverse effects in rats and mice treated with 75 mg/kg/day per os.

### **Pentoxiverine – R05BD03**

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

### **Oloxamine – R05DB07**

Patented in 1959.

We have been unable to locate references on possible human reproductive effects of this agent.

#### **Studies on laboratory animals**

- Nilsson (1967): nonteratogenic in mice (2 intravenous mg/day), but increased number of ribs.

### **Pipazetate – R05DB11**

Patented in 1961.

We have been unable to locate references on possible human reproductive effects of this agent, except for the survey by Heinonen et al (1977), or have we found any similar studies on laboratory animals.

#### **Prospective cohort studies with internal controls**

- Heinonen et al (1977), CPP: 1 healthy newborn exposed in the early 16 weeks.

### **Butamirate – R05DB13**

Patented in 1967.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

### **Dropropizine – R05DB19**

It is available in Italy since 1985.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

### **Cloperastine – R05DB21**

Patented in 1948.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

### **Morclofone – R05DB25**

Patented in 1970.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

### **Nepinalone – R05DB26**

It is available in Italy since 1994.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

### **Levodropropizine – R05DB27**

It is available in Italy since 1987.

We have been unable to locate references on possible human reproductive effects of this agent.

### **Studies on laboratory animals**

- Bestetti et al (1988): nonteratogenic in rats. Fetal toxic effects at 150 mg/kg/day.

### **Levocloperastine – R05DB49**

It is available in Italy since 1997.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

**R05BD Class Conclusions:** There are no specific studies relevant to the use in human pregnancy of agents belonging to this therapeutic class. In case of exposure the following arguments should be considered: the nature of these agents, the lack of reported anomalies

over the long period of commercialization, and the lack of teratogenic activity in laboratory animals.

## **R06 – Systemic Antihistamines**

These agents are competitive antagonists of histamine and block its receptors. They are divided into two groups: H1 and H2 blockers. The latest are employed in gastroenterology.

### **Systematic Review**

- Seto et al (1997): Medline and other relevant sources were examined to point out all controlled studies dealing with the frequency of congenital anomalies in first trimester exposures to antihistamines, over the period 1960-1991. 24 studies were found with about 2,000 exposures (Bunde and Bowler 1963; General Practitioner 1963; Mellin et al 1963; Nora et al 1967; Nelson and Forfar 1971; Ayd 1972; Milkovich and Van den Berg 1976; Kullander and Kallen 1976; Greenberg et al 1977; Heinonen et al 1977; Newman et al 1977; Smithells and Shepard 1978; Rothman et al 1979; Fleming et al 1981; Gibson et al 1981; Jick et al 1981; Eskenazi and Bracken 1982; Morelock et al 1982, Aselton and Jick 1983; Golding et al 1983; Michaelis et al 1983; Zierler and Rothman 1985; Seto et al 1993). The outcomes were altogether leading to a cumulative OR for major malformations of first trimester exposures to antihistamines = 0.8 (CI 95%: 0.6-0.9). This metanalysis brings strong evidence of no general risk increase of congenital anomalies. It unfortunately does not supply us with specific information relevant to some malformations.

The following general and specific studies do not include meta-analyzed studies of the above systematic review.

### **Prospective cohort studies with internal controls**

- Schatz et al (1997): A cohort study of 824 newborns to mothers suffering from asthma, and a cohort of 678 control newborns to non asthmatic mothers; both cohorts were interviewed prior to 28 weeks of gestation as per groups of drugs intake. Data were analyzed in consideration of different groups of drugs used in the treatment of maternal asthma and comparisons made between offspring exposed to a specific drug, vs. offspring not exposed to that drug but possibly exposed to another antiasthmatic medicament. 321 first trimester exposures to antihistamines; 1,175 nonexposed controls. 12 newborns exposed with congenital anomalies, vs. 65 out of the controls. RR = 0.7 (CI 95%: 0.4-1.2).
- Purohit et al (1985): the study wants to find out possible retrolental fibroplasia risk factors, not connected with oxygen therapy, on 3,025 pre-term infants with no congenital anomalies. Maternal diabetes and the intake of antihistamines in the last 2 weeks of gestation were detected (19 cases out of 86 exposures to antihistamines, vs. 324 out of 2,940 nonexposed newborns). RR = 2.0 (CI 95%: 1.3-3.1).
  - Diav-Citrin et al (2003), TIS Israel: 272 first trimester exposures to antihistamines, 844 controls. 8 newborns with congenital anomalies out of 272 exposures to antihistamines, vs. 25 out of 844 not exposed. RR = 1.0 (CI 95%: 0.5-2.2)

### **Case-control studies, specific**

- Shaw et al (1998), California BDMP: 538 cases of newborns with neural tube defect; 539 healthy controls. 21 exposed cases vs. 31 controls. OR = 0.7 (CI 95%: 0.4-1.2).
- Werler et al (1992): 76 cases with gastroschisis; 2,142 controls with other major

malformations. AOR for gastroschisis following first trimester exposure to antihistamines = 1.3 (CI 95%: 0.5-3.1).

### **Case-control studies, specific, nested in the prospective cohort study of all newborns**

- Kallen and Otterblad Olausson (2003), Swedish MBR: 5,015 cases of newborns with cardiovascular defects, out of which 189 exposures to antihistamines in the first trimester; 577,730 controls out of which 29,171 exposures. OR for cardiovascular defects = 0.8 (CI 95%: 0.7-0.9).
- Kallen (2003), Swedish MBR: 1,044 cases with non-syndrome cleft lip/palate, out of which 48 first trimester exposures to antihistamines; 576,873 (in overall) controls, out of which 29,155 exposures. OR = 0.9 (CI 95%: 0.7-1.2).

### **Diphenhydramine – D04AA13 – R06AA02**

This is amine-alkyl ether. Patented in 1947.

#### Case report

- Kargas et al (1996): 1 intrauterine death due to suspect pharmacological interaction between diphenhydramine and temazepam.

#### Cohort studies without controls

- Nageotte et al (1996): 80 exposures for hyperemesis. 3 newborns exposed, all in the second trimester, with congenital anomalies (Poland syndrome, feto-alcoholic syndrome, hydrocephaly with hypoplasia of right cerebral hemisphere)

#### Retrospective cohort studies with internal controls

- Rosa (1993), Michigan MSS: 1,461 first trimester exposures, 80 newborns with major defects, 62 expected. RR = 1.3 (CI 95%: 1.0-1.6).

#### Case-control studies, specific

- Saxen (1975), Finnish RCM: 599 newborns with facial schisis; 590 healthy controls. 20 exposures vs. 6 controls. OR = 3.4 (CI 95% : 1.3-9.4)

Feto-neonatal effects: exposed infants may suffer from withdrawal symptoms like tremors and diarrhea (Parkin 1974).

### **Clemastine – R06AA04**

This is amine-alkyl ether. It is available in Italy since 1987.

#### Retrospective cohort studies with internal controls

- Rosa (1993), Michigan MSS: 1,617 first trimester exposures, 71 newborns with major defects, 68 expected. RR = 2.6 (CI 95%: 0.6-0.9). 5 newborns with limbs hypoplasia vs. 1.9 expected. RR = 2.6 (CI 95%: 0.9-6.1).

#### Case-control studies, specific, nested in the prospective cohort of all newborns

- Kallen and Otterblad Olausson (2003), Swedish MBR: 18 newborns with cardiovascular defects exposed to Clemastine out of 5,015 cases; 1,997 exposures out of 577,530 controls. OR for first trimester exposure cardiopathy = 1.0 (CI 95%: 0.7-1.7).

### **Deschlorpheniramine – D04AA49 – R06AB02**

This is substituted alkylamine, dextrorotatory isomer of chlorpheniramine. Patented in 1962.

#### **Retrospective cohort studies with internal controls**

- Rosa (1993), Michigan MSS: 1,080 first trimester exposures, 50 newborns with major defects, 43 expected. RR = 1.2 (CI 95%: 0.8-1.5).

**Conclusions:** ADEC considers it a drug of choice in pregnancy.

### **Dimetindene – D04AA13 – R06AB03**

This is substituted alkylamine. Patented in 1960.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

### **Chlorphenamine (Chlorpheniramine) – R01BA99 – R06AB04**

This is substituted alkylamine. Patented in 1950.

#### **Retrospective cohort study with internal controls**

- Rosa (1993), Michigan MSS: 61 first trimester exposures, 2 newborns with major defects. 3 expected. RR = 0.7 (IC 95%: 0.1-2.7).

### **Pheniramine – R06AB05**

This is substituted alkylamine. Patented in 1951.

### **Tonzilamine – D04AA01 – R06AC06**

Ethyl endiamine substituted. It is available in Italy since 1990.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

### **Promethazine – D04AA10 – R06AD02**

Phenothiazine derivative. Patented in 1945.

#### **Retrospective cohort studies with internal controls**

- Rosa (1993), Michigan MSS: 1,197 first trimester exposures, 61 newborns with major defects, 51 expected. RR = 1.5 (CI 95%: 1.1-1.9).

### **Case-control studies, specific**

- Medveczky et al (2004), Hungarian CCSCA: 1,202 newborns with DTN, 34 of which exposed during the 2<sup>nd</sup> trimester of gestation (critical period for DTN); 38,151 healthy controls, 916 out of which exposed with OR = 1.2 (CI 95%: 0.8-1.6); 22,475 controls with other congenital anomalies, 600 out of which exposed with OR = 1.0 (CI 95%: 0.7-1.5).

### **Case-control studies, specific, nested in the prospective cohort of all newborns**

- Kallen and Otterblad Olausson (2003), Swedish MBR: 5,015 cases of newborns with cardiovascular defects, 41 exposed to promethazine; 577,730 controls, 4,759 exposures. OR for first trimester exposure cardiopathy = 1.0 (CI 95%: 0.8-1.4).

**Feto-neonatal effects:** neonatal tachycardia (Riffel et al 1973); respiratory distress in late pregnancy exposure (Crawford 1963), not recorded in three major studies (Potts and Ullery 1961, Carroll and Moir 1958, Powe et al 1962), thrombocytosis and withdrawal symptoms (contemporary exposure to more drugs, Nako et al 2001).

### **Mequitazine – R06AD07**

This phenothiazine derivative is available in Italy since 1985.

We have been unable to locate references on possible human reproductive effects of this agent.

### **Studies on laboratory animals**

- Maeda et al (1982): nonteratogenic in rats (1.25, 5 and 20 mg/kg per os) and rabbits (125 mg/kg per os).

### **Oxatomide – R06AE06**

Piperazine derivative. It is available in Italy since 1984.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

### **Cetirizine – R01BA52 – R06AE07**

This is piperazine derivative and metabolite of hydroxyzine. It is available in Italy since 1989.

### **Prospective cohort studies without controls**

- Wilton et al (1998): 16 healthy newborns exposed in the first trimester.

### **Prospective cohort studies with internal controls**

- Einarson et al (1997), TIS Motherisk: 39 exposures to cetirizine, 81 to hydroxyzine, and 110 controls. Lack of differences between groups according to their neonatal weight, gestation age, and congenital anomalies. 2 minor defects in 37 newborns exposed to cetirizine in the first trimester.

### **Case-control studies, specific, nested in the prospective cohort of all newborns**

- Kallen and Otterblad Olausson (2003), Swedish MBR: 5,015 cases of newborns with cardiovascular anomalies, 19 of which exposed to cetirizine; 577,730 controls, out of which 1,744 exposures. OR for first trimester exposure = 1.3 (CI 95%: 0.8-2.0).

### **Cyproheptadine – R06AX02**

It has been used as antagonist of serotonin to prevent recurrent miscarriage due to hyperserotoninem (Sadovsky et al 1970 and 1972). Patented in 1959.

### **Retrospective cohort studies with internal controls**

- Rosa (1993), Michigan MSS: 285 first trimester exposure, 12 newborns with major defects, 12 expected. RR = 1.0 (CI 95%: 0.5-1.7). RR for oral schisis = 3.3 (CI 95%: 0.4-12.0); RR for hypospadias = 2.8 (CI 95%: 0.3-10.3).

### **Terfenadine – R06AX12**

It has a long half-life of about 20-25 hours. Patented in 1975.

### **Retrospective cohort studies with internal controls**

- Rosa (1993), Michigan MSS: 1,034 first trimester exposures, 51 newborns with major defects, 44 expected. RR = 1.1 (CI 95%: 0.8-1.5).
- Loebstein et al (1999), TIS Motherisk: 118 exposures during pregnancy; no newborns with major defects, out of 65 first trimester exposures, vs. 2 among matched controls (RR = 0.6; CI 95%: 0.1-5.4). Low neonatal weight among exposed offspring.

### **Prospective cohort studies with internal controls**

- Schick et al (1994): 125 exposures in the first trimester and the beginning of the second trimester; 134 controls. 16 miscarriages (12.8%), 4 voluntary abortions, 98 healthy newborns, 1 stillbirth (0.8%). 6 newborns with congenital anomalies (4.8%) (2 chromosomal anomalies; persistent ductus arteriosus; hemangioma; ear lobe malformation, dysplasia of the hip).

### **Loratadine – R06AX13**

It is available in Italy since 1989.

### **Prospective cohort studies without controls**

- Wilton et al (1998): 16 healthy newborns exposed in the first trimester.

### **Prospective cohort studies with internal controls**

- Diav-Citrin et al (2003), TIS Israel: 210 exposures to Loratadine (126 in the first trimester), 267 to other antihistamines (146 in the first trimester), 929 nonexposed controls (844 in the first trimester). 1 newborn with congenital defect out of 126 exposed newborns to Loratadine, vs. 7 out of 146 newborns exposed to other antihistamines. RR = 0.3 (CI 95%: 0.0-1.9).
- Moretti et al (2003), 4 TIS: 161 first trimester exposures, 161 controls. 5 exposed newborns with congenital anomalies, vs. 6 among controls. RR = 0.8 (CI 95%: 0.3-2.7).

### **Case-control studies, specific, nested in the prospective cohort of all newborns**

Kallen and Otterblad Olausson (2003), Swedish MBR: 5,015 cases of newborns with cardiovascular anomalies, 18 of which exposed to loratadine; 577.730 exposures, 3.036 of which exposed. OR of cardiopathy for first trimester exposures = 0.7 (CI 95%: 0.4-1.1).

### **Ketotifen – R06AX17**

Patented in 1972.

We have been unable to locate references on possible human reproductive effects of this agent.

### **Studies on laboratory animals**

- Nakajima et al (1979): nonteratogenic in rats (30 mg/kg per os on days 7-17 and 17-21)

### **Acrivastine – R06AX18**

It is available in Italy since 1955.

### **Prospective cohort studies without controls**

- Wilton et al (1998): 22 healthy newborns exposed in the first trimester.

### **Mizolastine – R06AX25**

It is available in Italy since 1998.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

### **Fexofenadine – R06AX26**

It is available in Italy since 1998.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

**R06A Class Conclusions:** We have very large studies on intake of antihistamines or specific agents in the first trimester of pregnancy (in fact the systematic review by Seto et al alone comprehends about 200,000 exposures) and they did not reveal any increase in congenital anomalies. The positive outcomes observed by Rosa for diphenhydramine and promethazine should therefore be interpreted in this light. They would not alter the final result if included in the systematic review. ADEC and/or other organizations (American College of Obstetricians and Gynecologists 2000, American College of Allergology, Asthma and Immunology 2000), FASS and WGZ consider cyclizine, clemastine, cyproheptadine, chlorphenamine, cetirizine, diphenhydramine, pheniramine, meclizine, orciprenaline, and promethazine drugs of choice in pregnancy. There is only one slight misgiving that should be further surveyed: a specific association between oral schisis and diphenhydramine, suggested by Saxen. Finally, the study on retrolental fibrous dysplasia in pre-term deliveries and the use of antihistamines in the late weeks of pregnancy surely deserve to be done again. The hypothesis of Purohit, in fact, should

be considered as a simple suggestion to use caution in prospective prescription.

## **R07AB – Respiratory Stimulants**

### **Prectamide (Crotetamide + Cropropamide) R07AB06**

It is available in Italy since 1948.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

### **Dimeflin – R07AB08**

It is available in Italy since 1974.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

**R07AB Class Conclusions:** We have been unable to find any specific study in literature, relevant to the intake during pregnancy of agents belonging to this therapeutic class.