

## A- 3 Gastrointestinal System and Metabolism

### A02A – Antacids

These drugs are used to treat acid-related conditions. They do not influence the activity of acid-secreting cells but neutralize with a transitory effect the total acidity of the gastric juice. Chemical composition and capacity of neutralization distinguish them. They react to HCl forming chlorides, water and carbon dioxide. Antacids containing Al, Ca or Mg, have low systemic absorption.

#### Cohort studies without controls

- Jacobs (1975): no congenital anomalies were observed in the 48 pregnancies with first trimester exposure to antacids.

#### Case-control studies, nonspecific

Nelson and Forfar (1971): 458 newborns with congenital anomalies (175 major and 283 mild), 911 healthy controls; 27 newborns with congenital anomalies (12 with major anomalies) were exposed during the first trimester of pregnancy to antacids, vs. 24 healthy controls exposed to antacids (OR=2.3; IC 95% 1.3-4.2).

#### Case-control studies, specific

- Shaw et al (1988), California BDMP: 538 newborns with neural tube defects, 539 healthy controls (OR as per exposure to antacids = 0.6; IC 95%: 0.3-1.1).

**Feto-neonatal effects:** no adverse effects in the fetus following exposure to a number of antacids at different stages of pregnancy (Dordevic and Beric 1972, Mellin 1964, Royal College General Practitioners 1975).

### Magnesium Hydroxide – A02AA04

Only 5-10% of administered magnesium hydroxide is absorbed. It may cause hypercalcemia and hypermagnesemia. Available in Italy since 1951.

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

**Feto-neonatal effects:** no adverse effects have been shown in offspring exposed during the third trimester (Rudnicki et al. 1991).

### Algedrate (Aluminum hydroxide) –A02AB02

Algedrate aluminum chloride formed in the stomach is partially absorbed (15-30%). Subjects with renal impairment may accumulate aluminum in bones and CNS. It is available in Italy since 1967.

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

#### Studies on laboratory animals

- Gomez et al (1991), Colomina et al (1992): nonteratogenic in mice (up to 166mg/kg per os) or rats (up to 768mg/kg per os)

### **Colloidal aluminum phosphate – A02AB03**

Acting as a tampon, it is barely absorbed in intestine.

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.

### **Magaldrate anhydrous – A02AD02**

It is a compound of hydroxymagnesium aluminate, that reacting with gastric HCl is converted into aluminum and magnesium hydroxide. Aluminum hydroxide turns into aluminum chloride in the stomach and it is partially absorbed. It may determine hypercalcemia and hypermagnesemia. Subjects with renal impairment may accumulate aluminum in bones and CNS. Patented in 1955.

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

### **Studies on laboratory animals**

- Sakai and Moriguchi (1975) nonteratogenic in mice (up to 6000 mg/kg per os)

**Class A02A Conclusions:** The widespread use of these drugs during pregnancy, the absence of reports linking them to birth defects over the long period of commercialization, as well as the lack of systemic absorption, do not suggest that intake of antacids during pregnancy is associated with an increase of population background risk.

Nelson and Forfar study (1971) has uncovered an increase in population background risk of birth defects but, being not confirmed in further reports, it is probably biased by confounding factors, as the use of other drugs and maternal disease. The authors themselves suggested using results with caution. ADEC, FASS and WGZ consider antacids drugs of choice in pregnancy, except for those containing aluminum and sodium bicarbonate linked to a possible metabolic acidosis in both mother and offspring.

## **A20BA – Antagonists of H2 receptors**

These are histamine analogs. Highly hydrophilic, quickly absorbed per os, they inhibit in a competitive and dose-dependent way the acid secretion.

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

- Magee et al (1996), TIS Motherisk Program: 178 newborns exposed to antagonists of H2 receptors during pregnancy (126 of which to ranitidine) and as many controls; no differences between the two groups as per miscarriages or abortions, gestational age, birth weight and major malformations. (OR for congenital anomalies following exposure during pregnancy to antagonists of H2 receptors H2 = 0.7; IC 95%: 0.2-2.7).

### **Nested case-control studies, specific**

- Kallen and Otterblad Olausson (2003), Swedish MBR: 5,015 newborns with cardiovascular defects: 12 of them exposed to antagonists of H2 receptors during the first trimester. 577,730 controls 1,425 of which exposed. OR for cardiovascular defects = 1.0 (IC 95%: 0.5-1.7).

### **Cimetidine - A02BA01**

Patented in 1972.

### **Cohort studies without controls**

- Corazza et al (1982): 3 healthy newborns exposed during 16th, 12th and 31st week of gestation
- Lewis and Weingold (1985), manufacturer: 50 exposures during pregnancy over nonspecific periods; 3 newborns with congenital anomalies (cardiopathy; clubfoot; mental impairment).
- Koren and Zemlickis (1991), TIS Motherisk Program: 10 exposures over the first trimester: 8 healthy newborns (1 also exposed to ranitidine) and 2 ToP.

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

- Rosa (1993), Michigan MSS: 460 exposures during the first trimester; 20 newborns with major abnormalities, 20 expected (RR = 1.0; IC 95%: 0.6-1.5).
- Kallen (1998), Swedish MBR (1995-1997): 38 exposures during the first trimester; 2 newborns with congenital anomalies (encephalocele and unstable hip) (OR = 1.3; IC 95%: 0.3-5.1).

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

- Ruigomez et al (1999): 234 exposed newborns, 1,560 controls; 11 with congenital anomalies vs. 64 among the controls (RR adjusted for genetic abnormalities = 1.2; IC 95%: 0.6-2.3).

|                    |              |                  |              |                   |                 |
|--------------------|--------------|------------------|--------------|-------------------|-----------------|
| <b>Ruigomez et</b> | <b>Live-</b> | <b>Premature</b> | <b>Small</b> | <b>Still-born</b> | <b>Neonatal</b> |
|--------------------|--------------|------------------|--------------|-------------------|-----------------|

| <b>al 1999</b> | <b>born</b> | <b>birth</b> | <b>for date</b> |    | <b>deaths</b> |
|----------------|-------------|--------------|-----------------|----|---------------|
| Controls       | 1560        | 115(7.4%)    | 21              | 15 | 10            |
| Cimetidine     | 234         | 14(6.0%)     | 0               | 3  | 1             |

**Feto-neonatal effects:** no adverse effects were reported in newborns whose mothers had been treated with the drug at the end of pregnancy, to prevent pneumonia ab ingentis due to gastric aspiration. (McGowan 1979, Howe et al 1980, Johnson et al 1982, Husemeyer and Davenport 1980, Pickering et al 1980, Hodgkinson et al 1981, McCaughey et al 1981, Crawford 1981, Ostheimer et al 1982, Hodgkinson et al 1983, Quist and Storm 1983, Okasa et al 1983, Johnston et al 1983, Frank et al 1984, McAuley et al 1985. Thorburn and Moir, 1987). Hepatic transitory toxicity was reported in one newborn exposed during the third trimester of pregnancy (Glade et al 1980).

### **Ranitidine – A02BA02**

Patented in 1976.

#### **Cohort studies without control**

• **Cipriani et al (1986):** no adverse effects appeared in 3 newborns exposed throughout pregnancy.

- Koren and Zemlickis (1991), TIS Motherisk Program: 11 healthy newborns, 2 miscarriages and 1 haemangioma out of 14 exposures during the first trimester (1 also exposed to cimetidine).

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

- Rosa (1993), Michigan MSS: 516 exposures during the first trimester; 23 newborns with major abnormalities, 22 expected (RR=1.0; IC 95%: 0.7-1.6).
  - Kallen (1998), Swedish MBR (1995-1997): 176 exposures during the first trimester; 5 newborns with congenital anomalies (OR = 0.7; IC) 95%: 0.4-1.2).
- Ruigomez et al (1993): 330 exposures, 1,560 controls; 20 with congenital anomalies among the exposed vs. 64 among controls (RR=1.4; IC 95%: 0.8-2.4).

| <b>Ruigomez et al 1999</b> | <b>Live-born</b> | <b>Premature birth</b> | <b>Small for date</b> | <b>Still-born</b> | <b>Neonatal decease</b> |
|----------------------------|------------------|------------------------|-----------------------|-------------------|-------------------------|
| Controls                   | 1560             | 115 (7.4%)             | 21                    | 15                | 10                      |
| Ranitidine                 | 322              | 29 (8.8%)              | 2                     | 2                 | 1                       |

#### **Nested case-control studies, specific in the prospective cohort of all newborns**

- Kallen and Otterblad Olausson (2003), Swedish MBR: Cases = 5,015 newborns with cardiovascular defects, 10 of which exposed to ranitidine during the first trimester, 577,730 controls of which 1,041 exposed. OR for cardiovascular defects = 1.1 (IC 95%: 0.6-2.1).

**Feto-neonatal effects:** no adverse effects were reported in newborns whose mothers had been administered the drug at the end of pregnancy, to prevent pneumonia ab ingentis due to gastric aspiration (McAuley et al 1982,1983,1984; Gillett et al 1984; Mathews et al 1986; Ikenoue et al 1991; Rout et al 1993).

### **Famotidine – A02BA03**

Patented in 1979.

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

- Rosa (1993), Michigan MSS: 33 exposures during the first trimester; 2 newborns with major defects, 1 expected (RR=2.0; IC 95%: 0.2-7.2).

### **Nizatidine – A02BA04**

Available in Italy since 1987.

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

#### **Case report**

- **Gardner (1996):** 1 healthy newborn of 37 weeks exposed from 14th to 16th week after conception.

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

- Buelke - Sam (1989 a, 1989 b): nonteratogenic in rats (up to 1500 mg/kg per os), increase in fetal re-absorption, and decrease in fetal weight at maximum dose.

### **Roxatidine – A02BA06**

Available in Italy since 1992.

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

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

- Usui et al (1994): nonteratogenic in rats (up to 40-mg/kg e.v.).

**Class A02BA Conclusions:** The available studies on the intake of some drugs of this group do not suggest an increase in population background risk. Teratogenic effects over the long period of commercialization are not mentioned and in laboratory animals they are lacking (records provided by manufacturer for registration, not available in databases).

### **A02BB – Prostaglandin**

E2 and I2 prostaglandins (PGE2 and PGI2) are synthesized by gastric mucosa. They inhibit HCl formation and stimulate mucous and bicarbonate secretion. Slow-metabolization analogs of postglandins have been synthesized.

### **Misoprostol – A02BB01**

This is a synthetic analog of E1 prostaglandin and gastric mucosa protector. It is orally or vaginally administered at higher (800-16000 µg/die) than therapeutic (200-800 µg/die per os) doses as abortifacient, since it increases uterine contractions. Its abortive effectiveness is evaluated around 70% (Tang et al 1999) and in combination with mifepristone it is of 92.3-94% (WHO 2003). Patented in 1974.

#### **Case report**

- Collins and Mahoney (1983): 1 child with hydrocephaly and digit anomalies, born following failed pregnancy termination.
- Fonseca et al (1991): a total of 8 children were born with skull anomaly circumscribed to front-temporal area with exposure of dura madre and brain; they had been exposed to 400-1200 µg, during the first trimester to induce abortion.
- Gonzalez et al (1993): 7 children with limb malformations (artrogriposys, Moebius syndrome) exposed during the first trimester to 600-1800 µg.
- Gonzalez et al (1998): 42 children with limb abnormalities (equinovarus foot, arthrogryposis, and Moebius syndrome) due to vascular disruption exposed during the first trimester to an average dose of 800 µg (200-1600 µg).
- Hoffmeyr et al (1998): 1 child born with limb reduction defect; exposed during the 13th week to induce abortion.
- Genest et al (1999): one aborted fetus at 17<sup>th</sup> week with limb reduction defects and onphalocele; exposed to induce abortion.
- Coelho et al (2000): 15 patients with artrogriposis exposed to 400-4800µg between 8<sup>th</sup> and 12<sup>th</sup> week to induce abortion.
- Nunes et al (1999): 1 child with Moebius syndrome exposed to induce abortion.
- Sanchez and Guerra (2003): 1 child with Moebius syndrome exposed to 600 µg by vaginal way and 900 µg per os to induce abortion.

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

- Schuler et al (1992), TIS Brazil: 29 exposures to doses varying from 200 to 11,200 µg, with an average of 4,000 µg, during the first trimester. As a result: 3 pregnancies at the moment of issuing, 6 lost at follow-up, 3 miscarriages or fetal losses during 2<sup>nd</sup>-3<sup>rd</sup> trimester, 17 children were born without "major" malformations, 1 newborn had preauricular appendix.

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

- Castilla and Orioli (1994), ECLAMC: 5,708 children with congenital anomalies and as many controls; 8 children exposed with congenital anomalies vs. 4 among controls: (OR=2.0; IC 95%: 0.5-7.8). Despite the statistically negative outcome, investigators have observed that 4 out of 8 exposed defects, could be interpreted as defects due to embryo-fetal hypovascularization (1: phalanx absence, digit hypoplasia, partial syndactyly, peculiar facies, prominent nasal bridge, hypertelorism. 2: cleft lip and palate, hypertelorism, short limbs, bilateral absence of thumbs and fifth fingers, cutaneous appendix to right fingers, stiff knees, equinovarus foot. 3: gastroschisis. 4: cutaneous ulcer on T2-T3, without spina bifida).

#### **Cohort retrospective studies with internal controls**

- Rosa (19993), Michigan MSS: 1 cardiovascular defect out of 5 exposures during the first trimester, none expected; quite surely the drug was not administered to induce abortion.

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

- Schuler et al (1999), TIS Brasiliano: 86 exposed pregnancies, most probably to induce abortion, and as many not exposed controls; 2 children born with major congenital anomalies, out of 67 exposed newborns vs. 2 out of 81 controls, (RR=1.2; IC 95%: 0.28-4); 7 born with mild congenital anomalies out of 67 exposed children vs. 3 out of 81 controls; (RR=2.8; IC 95%: 0.8-1.5). No statistically significant differences for gestational age, neonatal weight, sex, premature birth and cesarean delivery.

## **Drugs and pregnancy**

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

- Pastuszek et al (1998): 96 case children with Moebius syndrome and 96 control children with neural tube defects, all born between 1990 and 1996 in Brazil; 47 of the cases were exposed vs. 3 exposed among the control. (OR=29.7; IC 95%: 11.6-76.0).
- Vargas et al (2000): 93 case newborns with vascular disruption anomalies and 279 controls with other congenital anomalies, all born in Brazil; 32 exposed among the cases vs. 23 among the controls: (OR=1.6; IC 95%: 0.9-2.8).
- Orioli and Castilla (2000), ECLAM: 4,673 case newborns with abnormalities likely to derive from embryo-fetal hypovascularization or anyway previously described in association with Misoprostol; 4,980 healthy control newborns, 34 exposed among the cases vs. 23 among the controls (OR= 1.7; IC95%: 0.9-2.8). Despite the statistically negative result investigators have analyzed specific anomalies and have observed a high number of exposures in 4 typical defects due to hypovascularization: cutaneous constrictions, limb reduction defects of transverse type, hydrocephaly and arthrogryposis.

### **Other studies**

- Bandim et al (2003): this is an atypical study, a case-control study just on children with Moebius syndrome: 7 out of 23 children with Moebius syndrome were affected by autism and 4 out of the 7 were exposed to Misoprostol. The study suggests a likely association between Misoprostol and autism in children having also Moebius syndrome.

**Conclusions:** Available studies, in particular case-control studies, specific and case reports, suggest a clear association between the use of Misoprostol during the first trimester and malformations of focal necrosis category, due to hypovascularization (i.e.: transverse type of limb reduction defects, Moebius syndrome). This, when the drug was used at high dosage, to induce abortion. Reported anomalies are sufficiently specific and consistent with the action of the drug. The more specific the anomaly, the higher the risk of congenital anomalies: in Moebius syndrome, the risk is 25 times higher while in the whole group of hypovascular-disruption defects (a pretty vague and inaccurate definition, therefore subdue to variations) the risk increases of 2-10 times. Nonetheless, the rareness of these defects implies that the attributable risk to exposure (AR) is so low, that it cannot be identified in cohort studies. For instance: AR is 1 out of 2,000 in Moebius syndrome, considering a risk increase equal to 25 and an incidence among general population of 1 out of 50,000. Or else: AR is 1 out of 1,000 for different hypovascular-disruption defects, considering a risk increase equal to 5 and an incidence among general population of 1 out of 5,000.

In case of exposure to high doses of Misoprostol, not followed by pregnancy termination, specific craniofacial and limbs echographies are suggested, in order to identify the possible, although infrequent impairments caused to the fetus.

## **A02BC – Acid pump inhibitor**

The final mediator of acid secretion is the so-called proton pump, in the membrane of stomach parietal cells. Inhibitors of proton pump (IPP) successfully inhibit acid secretion blocking H<sup>+</sup>K<sup>+</sup> - ATPase, an enzyme of the cell membrane. Inhibitors are liposoluble agents. They are quickly absorbed in the intestines, when administered orally.

### **Systematic review**

- Nikfar et al (2002): 6 cohort studies (Lalkin et al 1998, Kallen 1998-2001, Nielsen et al 1999, Ruigomez et al 1999, Moretti 2001 personal communication to the authors) 4 of which prospective, within a total of 593 pregnancies exposed to omeprazole and other inhibitors of the acid pump. Twenty-four congenital anomalies out of the total and other inhibitors of the acid pump, 15,330 controls, among which 774 congenital anomalies (RR, for congenital anomalies = 1.2; IC 95%: 0.7-1.9).

Cohort prospective studies with controls

- Nielsen et al (1999), PEP Database North Jutland: 38 women were administered IPP during the first trimester (35 had omeprazole; 3 had lansoprazole), 13,327 controls without prescription of refundable drugs from 1 month before pregnancy to the date of delivery. Major congenital anomalies were relevant among controls: 5.2%, and among the 38 subjects exposed to IPP there were 3 (7.9%) major congenital anomalies (DIV; piloric stenosis; arterial tube + DIA + hydrophrenosis + iris agenesis), (RR = 1.6; IC 95%: 0.5-5.2).

### **Nested case-control studies, specific**

- Kallen and Otterblad Olausson (2003), Swedish MBR: 5,015 cases of children born with cardiovascular defects, 16 of which exposed to IPP during the first trimester, 577,730 controls, 1,863 of which were exposed. (OR for cardiovascular defects = 1.0 (IC 95%: 0.6-1.7).

## **Omeprazole – A02BC01**

Available in Italy since 1990.

### **Systematic revisions**

- Nikfar et al (2002): see above. 4 cohort studies where only exposure to omeprazole had been investigated (Lakin et al 1998, Kallen 1998, Ruigomez 1999, Moretti 2001; personal communication to authors) have been considered: 534 pregnancies exposed to omeprazole, among which 19 congenital anomalies; 2,003 controls, among which 77 congenital anomalies (RR = 1.1; IC 95%: 0.6-1.9).

### **Case report**

- Tsirigotis et al (1955): 2 fetuses with congenital anomalies (1 had twisted foot and the other anencephaly), after GIFT pregnancy.
- Harper et al (1955): 3 healthy newborns from a woman who had taken ranitidine in her first pregnancy during 2<sup>nd</sup> and 3<sup>rd</sup> trimester; omeprazole during her second pregnancy from 11<sup>th</sup> week to birth; omeprazole and cimetidine throughout her third pregnancy.
- Rosa (1996): 11 congenital anomalies were reported to FDA in exposed fetuses, 4 of which were anencephalies and 1 hydrocephaly.

### **Cohort studies without controls**

- Bunner et al (1998): 9 children exposed at different stages of pregnancy (3 from conception to birth; 1 from conception to 8<sup>th</sup> week and from 28<sup>th</sup> week to birth; 5 during 2<sup>nd</sup> and 3<sup>rd</sup> trimester) were born without congenital anomalies. Follow-up evaluation from 2 till 12 years has shown a regular growth.

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

- Kallen (2001), Swedish MBR (1995-1999), an update of the 1998 study: 994 exposures: 863 during the first trimester; 131 during the third trimester of pregnancy, 39 exposed all over pregnancy. Congenital anomalies have been investigated, beside neonatal survival, neonatal weight and Apgar index. For all congenital anomalies (OR = 1.7; IC 95%: 0.5-1.3), for congenital anomalies of cardiovascular system (OR = 1.7; IC 95%: 0.5-3.9).

#### **Nested case-control studies, specific**

- Kallen and Otterblad Olausson (2003), Swedish MBR: 5,015 cases of children born with cardiovascular defects, 13 of which exposed to omeprazole during the first trimester, 577,730 controls among which 1,663 exposed. OR for cardiovascular defects = 0.9 (IC 95%: 0.6-1.6)

**Feto-neonatal effects:** this agent has been used as pre-medication for cesarean section without adverse effects in newborns (Moore et al 1989, Rocke et al 1994, Stuart et al 1996).

#### **Pantoprazole – A02BC02**

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.

#### **Lansoprazole – A02BC03**

Available in Italy since 1995.

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

- Wilton et al (1998): 7 healthy newborns following exposure during the first trimester

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

- Kallen (1998), Swedish MBR (1995-1997): 13 newborns following exposure, 2 with congenital anomalies (DIA, cryptorchidism). (OR=0.7%; IC 95%: 0.4-1.2)

#### **Rabeprazole – A02BC04**

Available in Italy since 1999.

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.

#### **Esomeprazole – A02BC05**

Available in Italy since 2002.

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.

**Class A02BC Conclusions:** A general reproductive risk is not likely when the subject has been exposed to pump inhibitors during pregnancy. This in consideration of: the wide range of available studies - particularly on some agents of this class, the failure to report teratogenic effects over the long period of commercialization, and the lack of teratogenic action on laboratory animals (records provided by manufacturer for registration, not available in databases).

## **A02BX – More antiulcer drugs**

### **Sucralfate – A02BX02**

This gastro-protector is composed of an alkaline aluminum complex of sulfated sucrose. By coating the stomach tissues it creates a protective barrier and promotes mucus and bicarbonates production. Only 2.2% of the administered dose is absorbed. Patented in 1965.

#### **Literature review**

- Lewis et al (1985), the American College of Gastroenterology reviewed the use of gastrointestinal drugs during pregnancy: sucralfate is a drug whose potential benefits exceed any potential risks.

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

- Rosa (1993), Michigan MSS: 183 first trimester exposures; 5 newborns had major defects, 8 expected: RR=0.6 (IC 95%: 0.2-1.5).

### **Pirenzepine – A02BX03**

This is an antagonist of muscarine receptors of the mioenteric plexus ganglions. Patented in 1962.

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

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

- Iida et al (1980-1986): no teratogenic actions have been uncovered in rats or rabbits.

### **Proglumide – A02BX06**

This agent is chemically related to glycoproteins in the gastric juice. Patented in 1965.

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

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

- Ishizaki et al (1971): neither major defects, nor postnatal alterations have been found in rats (3.350 mg/kg) and in mice (225 mg/kg), but an increase in vertebral anomalies and overnumbered hips has been uncovered.

### **Suglicotide – A02BX08**

This agent is chemically related to glycoproteins in the gastric juice. 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.

#### **Alginic acid – A02BX13**

It is a suspending agent generally used – as reported in its informative card – for “gastric pyrosis in pregnancy”. Available in Italy since 1982.

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.

**Class A02BX conclusions:** There is no written evidence of specific studies concerning the use of these antiulcer drugs. A general reproductive risk is not likely when the subject has been exposed. This, in consideration of the chemical characteristics of some agents of this class, the absence of reported teratogenic effects over the long period of commercialization and the lack of teratogenic action on testing on animals (records provided by manufacturer for registration, not available in databases).

#### **A03AA – Synthetic anticholinergic drugs, ester agents with tertiary amines groups**

These antispasmodics are being traded for a very long time.

#### **Mebeverine – A03AA04**

This drug has a direct action on the intestinal smooth muscle. Its action is not mediated by the autonomous nervous system and it therefore does not cause the usual side effects of other anticholinergic agents. 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.

#### **Trimebutine – A03AA05**

This is a gastroenteric peristalsis modulator, acting on Auerbach and Meissner plexuses; it has no central effects. Available in Italy since 1973.

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

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

- Asano et al (1982): nonteratogenic on neither rats nor rabbits (up to 1 mg/kg).

#### **Rociverine – A03AA06**

This agent has a direct myolytic papaverine-like action, selectively affecting visceral tissues, and a parasympholytic atropine-like action. It does not give rise to accumulation. Available in Italy since 1979.

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.

#### **Pipetanate ethidium bromide – A03AA49**

This agent is quickly absorbed in intestines and it gets over the ematoencephalic barrier. Available in Italy since 1996.

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.

### **A03AB – Synthetic anticholinergic, ammonia quaternary compounds**

These chemicals are ammonium quaternary compounds, ionized by physiologic pH, and as such they do not cross the placenta in significant quantities.

#### **Othylonium bromide – A03AB06 – A03CA04**

This is an antispasmodic. Only 3-5% of the intake is absorbed. Patented in 1966.

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.

#### **Prifinium bromide – A03AB18**

This is an antispasmodic. Available in Italy since 1979.

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

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

- Kumada et al (1972): nonteratogenic in rats (100 mg/kg per os), mice (50 mg/kg per os and 20 mg/kg subcutaneous) or rabbits (1 mg/kg per os).

### **A03AC – Synthetic antispasmodic, starches with tertiary amines**

#### **Tiropamide – A03AC05**

This is a synthetic antispasmodic. Patented in 1974.

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

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

- Shimazu et al (1992): nonteratogenic in rats (100 mg/kg per os).

**Class A03AB-A03AC conclusions:** No specific studies are available in literature consistent with the use of agents of these therapeutic classes in human pregnancy. In case of exposure an increase in the background reproductive risk is not likely, due to a lack of reported anomalies over the long period of commercialization and considering that teratogenic effects in laboratory animals have not been found (records provided by manufacturer for registration, not available in databases).

#### **Papaverine – A03AD01**

This is a vasodilator, antispasmodic opium alkaloid. Available in Italy since 1951.

#### **Cohort prospective studies with internal controls**

- Heinonen et al (1977), CPP: 2 healthy newborns exposed during the first 16 weeks.

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

- Lee and Natele (1979): a neural tube fastening defect has been noticed in chicken rearing at 50 mg/ml.
- Jurand (1980): a twist tale or the widening of the 3<sup>rd</sup> ventricle in 5% of the cases has been shown in mice (140 mg/kg subcutaneous, 5 times the maximum human dose).

**Conclusions:** There is no written evidence of specific studies concerning the use of agents of these therapeutic classes in human pregnancy. In case of exposure an increase in the background reproductive risk is not likely, due to a lack of reported anomalies over the long period of commercialization. On the ground of these considerations ADEC, FASS and WGZ reckon it a drug of choice in pregnancy.

### **A03AX – Other drugs for functional intestinal diseases**

These agents have been on the market for over 20 years.

#### **Pinaverium – A03AX04**

This is an antispasmodic. It appears to be scarcely absorbed in gastrointestinal apparatus. Available in Italy since 1986.

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

- Einarson et al (1999): 10 exposed pregnancies, 5 during the first trimester, 5 from the 12<sup>th</sup> to the 16<sup>th</sup> week, 9 healthy newborns, and 1 miscarriage.

#### **Proxazole – A03AX07**

This is a peripheral vasodilator. Patented in 1959.

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.

#### **Floroglucinole – A03AX12**

This is an antispasmodic agent, a directly acting myolytic. Available in Italy since 1962.

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.

**Feto-neonatal effects:** there has been no evidence of adverse effects (no premature birth threatening, no travail problems), both in mothers and/or offspring, following its use late in pregnancy. (Morin et al 1964, Plasse et al 1964, Foti et al 1971).

#### **Dimethicone (Simethicone) – A03AX13**

This agent is used to prevent meteorism. It is a silicon derivative and it is not absorbed by the gastroenteric apparatus. Patented in 1948.

Cohort retrospective studies with internal controls

- Rosa (1993), Michigan MSS: 248 exposures during the first trimester, 14 had major defects, 11 expected. (RR = 1.3; IC 95%: 0.7-2.1).

#### **Meglucinole– A03AX99**

This is an antispasmodic. Available in Italy since 1969.

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.

**Class A03AX conclusions:** pretty limited specific studies have been located in literature, or else they are lacking at all, consistent with the use of some of the drugs belonging to this class in human pregnancy. In case of exposure an increase in the background reproductive risk is not likely, due to absent (simethicone) or insufficient (pinaverium) intestinal absorption. In addition, a lack of reported anomalies over the long period of commercialization is to be

considered, as well as the absence of teratogenic action on laboratory animals (records provided by manufacturer for registration, not available in databases).

### **A03BA – Belladonna alkaloids**

#### **Atropine – A03BA01**

This is an anticholinergic drug. It is a solanaceae extract, mainly from *Atropa Belladonna*. Patented in 1900.

#### **Case report**

- Siebert et al (1989): 1 newborn with multiple congenital defects exposed to atropine and diphenoxylate during the 10<sup>th</sup> week of pregnancy. The exposure period does not coincide with the embryonic development of the noticed defects.

#### **Cohort retrospective studies with internal controls**

- Rosa (1993): Michigan MSS. 381 exposures during the first trimester; 18 with major defects, 16 expected: (RR = 1.1; IC 95%: 0.7-1.8).

#### **Cohort prospective studies with internal controls**

- Heinonen et al (1977), CCP: 401 exposures during the first 16 weeks; 17 newborns with congenital anomalies: (ARR = 0.9; IC 95%: 0.5-1.4).

**Feto-neonatal effects:** 1 newborn has been reported to show mydriasis, exposed over the last period of pregnancy to high doses administered as an antidote to the maternal attempted suicide with organ-phosphate ester (Shan et al 1995). Its use, in the imminence of the delivery, might determine a reduction in breath rate and bradycardia (Roodenburg et al 1979). Some authors, though (Diaz et al 1980, Roper and Salem 1981, Abboud et al 1983), have not found any significant change neither in the pulse rate nor in the uterine contractility, in women treated with atropine e.v. before childbirth.

**Conclusions:** The available studies on the exposure during the first trimester and the vast clinical experience do not show any increase in the background reproductive risk. ADEC, FASS and WGZ consider it a drug of choice in pregnancy.

### **A03B – Belladonna and its derived agents**

#### **A03BB – Semi-synthetic belladonna alkaloids, quaternary ammonium compounds**

Synthetic and semi-synthetic alkaloids of belladonna are quaternary ammonium compounds. Quaternary ammonium compounds are ionized at physiologic pH. They are barely absorbed when administered orally and do not cross the placenta in significant quantities. These drugs have been marketed for over 30 years.

#### **Butylscopolamine (scopolamine butylbromide, hyoscine butylbromide – A03BB01 – A03DB04**

This is an antispasmodic and anticholinergic analog of atropine. It readily crosses the placenta. Patented in 1950.

#### **Cohort prospective studies with internal controls**

- Heinonen et al (1977), CCP: 79 exposures during the early 16 weeks; 2 newborns with congenital anomalies: (ARR = 0.6; IC 95%: 0.1-2.3).

**Feto-neonatal effects:** Several cases have been reported over the period 1952-1959 on the use of this drug after the first trimester, with no adverse effects in offspring (Onnis et al 1983).

**Cimetropium bromide – A03BB05**

It is an anticholinergic, spasmolytic agent. Patented in 1972.

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

**Studies on laboratory animals**

- Matsuo et al (1977): nonteratogenic neither in rats nor in rabbits (1000 mg/kg per os).

**Conclusions:** There is no written evidence of specific studies concerning the use of agents in this therapeutic class in human pregnancy. In case of exposure an increase in the background reproductive risk is anyway not likely, due to a lack of reported anomalies over the long period of commercialization. The pharmacological characteristics and the absence of teratogenic action on laboratory animals should be also considered (records provided by manufacturer for registration, not available in databases).

### **A03CA - Synthetic anticholinergic drugs in association with psycholeptics**

These quaternary ammonium compounds are ionized at physiologic pH. They are little absorbed when administered orally and do not cross the placenta in significant quantities.

#### **Isopropamide iodide – A03CA01**

It is an antispasmodic. Patented in 1954.

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

- Heinonen et al (1977), CPP: 180 exposures during the early 16 weeks; 9 had congenital anomalies. (ARR = 1.1; CI 95% 0.6-2.1).

#### **Clidinium bromide – A03CA02**

It is an antispasmodic. Patented in 1951.

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

- Heinonen et al (1977), CPP: 4 exposures during the early 16 weeks. Clidinium has been analyzed during the early 16 weeks along with other parasympatholytic drugs in 60 exposures altogether, uncovering 2 newborns with congenital anomalies. (ARR for the whole group = 0.7; CI 95%: 0.2-2.9).

#### **Propantheline bromide – A03CA34**

It is an antispasmodic. Patented in 1950.

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

- Heinonen et al (1977), CPP: 33 exposures during the early 16 weeks, 1 with congenital anomalies. (ARR 0.7; CI 95%: 0.1-4.6).

#### **Octatropine methylbromide (anisotropine) – A03CB49**

It is an antispasmodic. Patented in 1957.

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

- Heinonen et al (1977), CPP: 2 exposures during the early 16 weeks. Octatropine has been analyzed during the early 16 weeks along with other parasympatholytic drugs in 60 exposures altogether, uncovering 2 newborns with congenital anomalies. (ARR for the whole group = 0.7; CI 95%: 0.2-2.9).

**Class A03CA conclusions:** Only limited studies are available in literature, consistent with the use of agents of this therapeutic class. In case of exposure an increase in the background reproductive risk is not likely. This, in consideration of its little absorption and transplacental crossing and also due to a lack of reported anomalies over the long period of commercialization, their pharmacological characteristics and the absence of teratogenic action on laboratory animals (records provided by manufacturer for registration, not available in databases).

### **A03FA – Prokinetics**

Gastric motility depends on the stimulation from cholinergic neurons, inhibition from adrenergic neurons and dopamine and serotonin action. Prokinetics aiming at correcting gastric motility are antagonists of dopaminergic receptors (D2) and 5-HT and agonists of 5-HT receptors. These drugs have been on the market for about 15-20 years. The "father" of this group of drugs, metoclopramide, has been fully studied.

### **Metoclopramide – A03FA01**

This is an antiemetic, a competitive antagonist of dopamine receptors (D2) and of serotonin 5-HT. Patented in 1961.

#### **Case Report**

- Milo et al (1989), Guikontes et al (1992), Tincello and Johnstone (1996), Shenhav et al (1977): 4 healthy newborns exposed during the late weeks of the first trimester.

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

- Notter and Theoleyre (1967) (quoted by Onnis 1983): 18 first trimester and 9 second trimester exposures; no teratogenic or embryo-feto-toxic effects were reported).
- Migliavacca et al (1968) (quoted by Onnis 1983): 70 first trimester and 20 second and third trimester exposures; no teratogenic or embryo-feto-toxic effects were reported.
- Catizone and Romano (1968) (quoted by Onnis 1983): 21 first trimester exposures; no teratogenic effects were reported.
- Nageotte et al (1996): 80 exposures between 10.9  $\square$  3.9 weeks; no teratogenic effects were reported.

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

- Rosa (1993), Michigan MSS: 192 first trimester exposures; 10 newborns with major defects, 8 expected: RR = 1.2 (CI 95%: 0.6-2.3).
- Sorensen et al (2000), PEP Database North Jutland: 309 exposures and 13,327 controls; no differences among groups as per congenital anomalies (OR = 1.1; CI 95%: 0.6-2.1), neonatal weight (OR = 1.8; CI 95%: 0.8-3.9) and prematurity (OR = 1.0; CI 95%: 0.6-1.7).

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

- Sidhu and Lean (1970), clinic trial to evaluate antiemetic effects: 120 pregnant women at less than 28 weeks; 25 healthy newborns exposed to metoclopramide.
  - Berckovitch et al (2000) (2002), 6 TIS: 175 first trimester exposures, 175 not exposed controls; no difference between the two groups as per congenital anomalies (RR = 0.9; CI 95%: 0.3-2.4), spontaneous abortions (RR = 0.8; CI 95%: 0.2-2.9), gestational age and neonatal weight. Prematurity percentage among the exposures appeared to be higher (RR = 3.4; CI 95%: 1.1-10.1).

**Feto-neonatal effects:** Metoprolamide has been used at childbirth to prevent pneumonia ab ingentis due to gastric reflux (Bylsma et al 1983, Cohen et al 1984, McGarry 1971, Howard and Sharp 1973, Brock et al 1978, Hey and Ostik 1978, Feeney 1982, Murphy et al 1984, Vella et al 1985, Shenhav et al 1997, Orr et al 1993 and Stuart et al 1996) and during second and third trimester (Notter and Theoleyre 1967, Migliavacca et al 1968) without any adverse effect in newborns.

**Conclusions:** The available studies on first trimester metoprolamid exposure do not uncover any increase in background reproductive risk. ADEC, FASS and WGZ consider it a drug of choice in pregnancy.

### **Domperidone – A03FA03**

This is an antiemetic, benzimidazole derivative. It acts as a dopaminergic antagonist on peripheral level. It has extrapyramidal and endocrine side effects on

adults (amenorrhea, galactorrhea, and hyperprolactinemia) and it is dose-dependent. Patented in 1975.

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

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

- Hara et al (1980): skeleton and eye defects (200 mg/kg) skeleton defects and reduced intrauterine growth (30 mg/kg e.v.) in rats; decreased survival but no congenital anomalies (25 mg/kg) in rabbits. Rats were exposed to 100 times the dose used in human therapies (30-40 mg/die per os).

**Conclusions:** There is no written evidence of specific studies concerning the use of domperidone in human pregnancy. In case of exposure an increase in the background reproductive risk is not likely, due to a lack of reported anomalies over the long period of commercialization. Studies on laboratory animals, rats exposed to 100-150 times the dose used in human therapies, have established a teratogenic action, whereas such findings have not been identified in rabbits administered 10-15 times the dose used in humans.

#### **Bromopride – A03FA04**

This is a spasmolytic and antiemetic drug, metoclopramide derivative. It increases acetylcholine release in the plexus mio-entericus. Patented since 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.

#### **Alizapride – A03FA05**

This is an antiemetic drug, antagonist of dopamine receptors. It has extrapyramidal and endocrine side effects on adults (amenorrhea, galactorrhea, and hyperprolactinemia) and it is dose-dependent. 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.

#### **Clebopride – A03FA06**

This is an antiemetic, anti-dopaminergic and serotonergic drug. It has extrapyramidal and endocrine side effects on adults (amenorrhea, galactorrhea, and hyperprolactinemia) and it is dose-dependent. Available in Italy since 1988.

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

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

- Kawana et al (1982): nonteratogenic in rats nor in rabbits (100 mg/kg/die per os)

#### **Levosulpiride – A03FA49**

This is an antidiarrheal, antiemetic and anti-dopaminergic of synthesis. It has extrapyramidal and endocrine side effects on adults (amenorrhea, galactorrhea, and hyperprolactinemia) and it is dose-dependent. 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.

**Class A03FA conclusions:** No specific studies are available in literature consistent with most of prokinetics use in human pregnancy, except for

metoprolamide that has been fully studied. In case of exposure an increase in the background reproductive risk is not likely, due to a lack of reported anomalies over the long period of commercialization and the absence of teratogenic action on laboratory animals (except for domperidone, see) (records provided by manufacturer for registration, not available in databases). A teratogenic effect on rats, but not on rabbits, has been reported, nonetheless this has little predictive value and it does not affect the achieved conclusions.

## **A04A – Antiemetic and anti-nausea drugs**

The nervous center of vomiting receives stimuli from different cerebral areas and from visceral afferent originating in the peripheral area. Dopaminergic receptors (D2), serotonin receptors (5-HT) and muscarinic receptors of gastrointestinal tract mediate the inhibition of gastric motility that occur during nausea and vomiting. Dopamine, serotonin and acetylcholine are important emetic transmitters but when the transmission is blocked, there is a rise of antiemetic effects.

### **A04AA – Serotonin antagonists (5HT3)**

#### **Ondasetrone – A04AA01**

Available in Italy since 1992.

Case report

- Guikontes et al (1992): 1 healthy newborn exposed to dimenidrinat, metoclopramide (6<sup>th</sup>, 10<sup>th</sup> week) and ondasetrone (11<sup>th</sup> –13<sup>th</sup> week).
- World (1993): 1 exposure from 30<sup>th</sup> to 33<sup>rd</sup> weeks.
- Tincello and Johnstone (1996): 1 healthy newborn exposed to prometazine, prochlorperazine, metoclopramide (8<sup>th</sup> –13<sup>th</sup> week) and ondasetrone (14<sup>th</sup> –33<sup>rd</sup> week)
- Siu et al (2002): 1 healthy newborn exposed during the first trimester due to maternal iperemesis to metoclopramide, prometazine (5<sup>th</sup> –12<sup>th</sup> week) and ondasetrone (13<sup>th</sup> –14<sup>th</sup> week).

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

- Einarson A. et al (2004), TIS Motherisk Program and Mothersafe Program in Sidney, Australia: 169 exposures to ondasterone with 6 congenital major defects. No differences between the two control groups of similar size (a) exposed to other anti-nausea drugs and (b) exposed to agents commonly believed nonteratogenic.

#### **Granisetrone – A04AA02**

Available in Italy since 1992.

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

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

- Baldwin at al (1990): nonteratogenic in rats (9mg/kg e.v) or in rabbits (3mh/kg e.v.)
- Baldwin et al (1993): nonteratogenic in rats (100 mg/kg per os).

Feto-neonatal effects: no problems have been reported consistent with exposures after the first trimester (Merimsky and Le Cesne, 1998, Merimsky et al 1999).

#### **Tropisetrone – A04AA03**

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.

#### **Dolasetrone – A04AA04**

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.

**Class A04AA conclusions:** There is no written evidence of specific studies concerning the use of agents of this therapeutic class. In case of exposure, in spite of their little use in pregnancy, an increase in the background reproductive risk is not likely. This, in consideration of a lack of reported anomalies over the long period of commercialization and the absence of teratogenic action on laboratory animals (except for domperidone, see) (records provided by manufacturer for registration, not available in databases).

## **A04AD – Other antiemetic drugs**

### **Scopolamine – A04AD01**

It is an anticholinergic, analog of atropine and it impedes gastrointestinal muscarinic receptors.

#### **Retrospective cohort studies with internal control**

- Rosa (1993), Michigan MSS: 27 first trimester exposures; 1 with major defect, one expected (RR = 1.0; CI 95%: 0.6-5.6).

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

- Heinonen et al (1977), CPP: 309 exposures during the early 16 weeks; 14 with congenital anomalies (ARR = 1.0; CI 95%: 0.6-1,7)

**Feto-neonatal effects:** its use over the late period of pregnancy may determine tachycardia and alterations of fetal rhythm (Shenker 1973, Boehm and Growdon 1974 and Ayromlooi et al 1980) as well as tachycardia and neonatal lethargy (Evens and Leopold 1980).

**Conclusions:** We have not found yet any evidence of association between scopolamine and the increase in background reproductive risk. In case of exposure an increase in the background reproductive risk is not likely, due to a lack of reported anomalies over the long period of commercialization and the absence of teratogenic action on laboratory animals (records provided by manufacturer for registration, not available in databases).

### **Dimenhydrinate – A04AD49**

It is an antihistaminic, a chloroteofillinic salt of diphenhydramine. It is an ethanolaminic derivative and a stopper of H1 receptors of histamine. It acts by impeding gastrointestinal muscarinic receptors. Patented in 1949.

#### **Cohort studies without control**

- Gross et al (1989): 64 exposures during the early 13 weeks, for hyperemesis; 1 newborn with syndactyly, 2 newborns with cutaneous appendix (auricular and sacral).

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

- Heinonen et al (1977), CPP: 319 exposures during the early 16 weeks; observed? (ARR for any type of malformation = 0.9; CI 95%: 0.5-1.5).

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

- Mellin and Katzstein (1936): 266 newborns with congenital anomalies. No differences between the two groups as per exposure in pregnancy.

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

- Medveczky et al (2004), Hungarian CCSCA: of 1,202 newborns with NTD, 31 second trimester exposures (critical period for NTD); of 38,151 healthy

controls, 883 exposures with OR = 1.1 (CI 95%: 0.8-1.6); of 22,475 controls with other congenital anomalies, 452 exposed with OR = 1.3 (CI 95%: 0.9-1.9).

**Conclusions:** The available studies on dimenhydrinate exposure during the first trimester do not reveal an increase in the background reproductive risk. ADEC and FASS consider this agent an antiemetic of choice.

### **Prochlorperazine – A04AD49 – N05AB04**

It is a piperazinic phenothiazine, acting as a stopper of dopaminergic receptors (D2). Patented in 1954.

#### **Case report**

- Hall (1963): 1 newborn, also exposed at the beginning of gestation to other phenothiazines, showing hypo-agenesia of upper limbs.
- Freeman (1972): 1 newborn exposed at the beginning of gestation showing limbs hypo-agenesia.
- Ho et al (1975): 1 newborn with multiple malformations (cleft palate, micrognathia, cardiopathy, hypo-agenesia of lower limbs, polydactyly and hip dysplasia) exposed during the first trimester to different drugs, including prochlorperazine (combine estrogens, bendectin, aspirin, acetaminophen, salicylamide, caffeine, chlorpromazine, diphenoxylate and atropine).
- Farag and Ananth (1978): 1 newborn exposed during the first trimester showing limb hypo-agenesia.
- Rafla (1987): 2 pregnancies (3 newborns) exposed during the early 12 weeks; two newborns with limb defects (mutilation below the elbow with little and atrophic hand; one of the twins with a mutilation below the knee with rudimentary /rough?/ foot).

#### Cohort studies without control

- Sullivan (1958): 80 first trimester exposures; none with congenital anomalies
- Farkas and Farkas (1971): 41 newborns only exposed to prochlorperazine during the first trimester; none with congenital anomalies. 162 exposures during the first trimester to the association of chlorpromazine + promethazine + prochlorperazine with no increase of congenital anomalies (0.61%).
- Milcovich and Van Den Berg (1976): 433 pregnancies exposed during the first trimester. No increase of congenital anomalies in neither newborns nor children with follow-up until 5 years of age.

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

- Nelson and Forfar (1971): Cases: 175 newborns with "major malformations" and 283 with "mild malformations". Controls: 911 newborns without malformations. Exposed: 2 among the newborns with "major malformations" and 7 among the newborns with "mild malformations" in the first trimester vs. 15 among controls (OR for malformations in overall = 1.2; CI 95%: 0.5-2.9).

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

- Rosa (1993), Michigan MSS: 704 first trimester exposures; 24 newborns with major defects, 29 expected (RR = 0.8; CI 95%: 0.5-1.2).

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

- Heinonen et al (1977), CPP: 877 exposures during the early 16 weeks; 47 with congenital anomalies: (ARR = 1.0; CI 95%: 0.5-2.9).

**Feto-neonatal effects:** Exposure to fenotiazine over the late period of pregnancy may determine extrapyramidal symptoms (Hill et al 1966, Anath 1976) as well as withdrawal symptoms (irritability, choreic and dystonic movements, hypertonia, restlessness) which can persist even up to six months (O'Connor 1981, Simpson et al 1981). Besides, hyperbilirubinemia and jaundice of the newborn may be observed (Simpson et al 1981) and also intraocular melanina deposit (Ullberg et al 1970).

**Conclusions:** Available studies on first trimester prochlorperazine exposure do not confirm the case reports hypothesis of association with hypo-agenesia of limbs, or do they suggest any increase in the background reproductive risk. Feto-neonatal side effects have been reported late in pregnancy exposures.

**Tietilperazine – A04AD49 – R06AD03**

It is a phenotiazinic derivative and it acts blocking dopaminergic receptors (D2). Patented in 1956.

**Case report**

There is a large number of reports over the years 1963-66, quoted by Onnis et al (1983), about the use of this agent both in the first and in the following trimesters with no adverse effects in offspring.

**Case-control studies, specific**

- Czeizel and Varga (2003), Hungarian CCSCA: 22,843 case newborns with congenital anomalies; 38,151 healthy controls. 411 first trimester exposures among cases, vs. 746 among controls OR = 0.9; CI 95%: 0.8-1,1. The sole association to be noticed among at least 18 defects or defect classes: labio +/- cleft palate (OR = 2.0; CI 95%: 1.0-4.0), that should anyway be interpreted as random, considering the multiple matching carried out (see below).

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| <b>Defects</b>            | <b>OR</b> | <b>CI 95%</b> |
|---------------------------|-----------|---------------|
| NTD                       | 1.1       | 0.6-2.1       |
| LS □ PS                   | 2.0       | 1.0-4.0       |
| Cleft Palate              | 1.6       | 0.5-4.9       |
| Pyloric Stenosis          | 0.8       | 0.1-5.8       |
| Obstructed Urinary Tract  | 2.4       | 0.7-8.3       |
| Hypospadias               | 1.3       | 0.8-2.0       |
| Cryptorchidism            | 1.5       | 0.7-3.1       |
| Onphalocele/Gastroschisis | 0.7       | 0.2-2.8       |
| Hydrocephalus             | 2.5       | 0.4-15.5      |
| Ear anomalies             | 0.3       | 0.1-1.2       |
| Cardiovascular defects    | 0.9       | 0.6-1.4       |
| Clubfoot                  | 1.2       | 0.8-2.0       |
| Limbs Hypo-agenesia       | 0.9       | 0.3-3.0       |
| Poli-syndactyly           | 1.0       | 0.5-1.8       |
| Skeleton defects          | 0.4       | 0.1-1.6       |
| Diaphragm defects         | 2.6       | 0.2-30.1      |
| Other isolated defects    | 0.7       | 0.3-1.3       |
| Multiple defects          | 1.0       | 0.5-2.0       |

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**Prospective cohort studies with internal controls**

- Heinonen et al (1977), CPP: 71 exposures to different phenotiazine, 19 of which to tietilperazine, during the early 16 weeks; 5 newborns with congenital

anomalies (ARR = 1.6; CI 95%: 0.7-3.6). Of 1,309 exposures to phenothiazine, 66 newborns had congenital anomalies (ARR = 1.0; CI 95%: 0.9-1.4).

**Case-control studies, specific**

- Medveczky et al (2004), Hungarian CCSCA: 1,202 newborns with NTD, 16 of which exposed during the second trimester (critical period for NTD); of 38,151 healthy controls, 368 exposures with OR = 1.3 (CI 95%: 0.8-2.2); 22,475 controls with congenital anomalies, 171 of which were exposed with OR = 1.7 (CI 95%: 0.9-2.8).

**Conclusions:** We have not located any association between tetilperazine and background reproductive risk. In case of exposure the risk increase is not likely, considering the available studies on humans and that the fenothiazine class has been fully studied. Besides, reported anomalies over the long period of commercialization are lacking and there is no evidence of teratogenic action on laboratory animals (records provided by manufacturer for registration, not available in databases).

## **A05 – Biliary and hepatic therapy**

### **A05A – Biliary therapy**

#### **A05AA – Bile acids-based compounds**

Biliary acids and their conjugates are essential components of bile. They are water-soluble agents of cholesterol metabolism and are used as cholagogues to increase bile production.

#### **Ursodeoxycholic acid – A05AA02**

It is a litholytic, normally present in the bile. It is absorbed in the small intestine and conjugated by liver: the continuous resorption from the portal vein to the liver (enterohepatic circulation) and the strong protein binding suggest that there is no hepatic passage (Bacharach and Hoffman 1982). Patented in 1963.

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

#### **Case report**

- Rudi et al (1996): 1 healthy newborn exposed over pregnancy.
- Axcan Pharma (2000): 4 first trimester exposures; no adverse effects in offspring.
- Krunchkovich and Blickstein (2003): 1 healthy newborn exposed over pregnancy.

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

- Toyoshima et al (1978): non teratogenic in rats (22mg/kg/die)

Feto-neonatal effects: the use of this agent in 130 exposures during the third trimester to treat cholestasis of pregnancy has not revealed unwilling outcomes in the newborn. (Mazzella et al 1991, Palma et al 1992, Floreali et al, 1994, Davies et al 1995, Diaferia et al 1996, Palma et al 1997, Calmelet et al 1998, Corakci et al 1998, Gronlund 1999, Berkane et al 2000, Laifer et al 2001, den Dulk et al 2002, Lengyel et al 2002, Milkiewicz et al 2003).

#### **Chenursodeoxycholic acid – A05AA49**

This is a litholytic compound, biliary acid-based. It is a synthesis agent, similar to the natural bile compounds (chenodeoxycholic and ursodeoxycholic acids). 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.

#### **Tauroursodeoxycholic acid – A05AA49**

This is a litholytic agent, a normal conjugate of ursodeoxycholic acid in human bile and it is one of the bile acid of the enterohepatic circulation. Available in Italy since 1992.

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.

#### **Hymecromone – A05AX02**

It is a choleric, cholagogue, spasmolytic and atropinic agent. Available in Italy since 1984.

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

Studies on laboratory animals

- Taddei (1967): nonteratogenic either in mice or rabbits at 50-200-800 mg/kg, or else in rats at 50-200-1200 mg/kg.

#### **Phenylpentol – A05AX49**

It is a choleric, phenylpropanol derivative. 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.

**Class A05A conclusions:** We have not located any reference on the use of drugs of this class in human pregnancy. In case of exposure the population-based risk increase is not likely, considering the lack of reported anomalies over the long period of commercialization, their pharmacological characteristics and the absence of teratogenic action on laboratory animals (records provided by manufacturer for registration, not available in databases).

#### **A05B – Hepatic therapy, lipotropics**

##### **Silymarin – A05BA03**

This is an hepato-protective substance, extracted from Silybum Marianum. Patented in 1968.

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

##### **Case report**

- Boyer et al (2001): 1 first trimester exposure, following maternal amanita phalloides poisoning.

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

- Hahn et al (1958): nonteratogenic in rats (1,000 mg/kg) or in rabbits (100 mg/kg).

##### **Ornithine ossoglurate – A05BA06**

Ornithine is an important component of the Krebs-Henseleit cycle.

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.

##### **Ademetionine – A05BA49**

This is a combination of methionine and adenosine. It stimulates transmethylation processes, hence activating the hepatic detoxification. Synthesized in 1952.

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.

##### **Cogalactoisomerase (uridin-5-diphosphoglucose) – A05BA49**

Uridin-5-diphosphoglucose is used in glucuronoconjugation processes of very many endogenous and exogenous agents. Available in Italy since 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.

**Phosphatidilcoline– A05BA49 – C10AX49**

It is a hypolipidemic and a cholinic ester of different phosphatidic acids. Physiologically present in animals. 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.

**Thymonacic– A05BA49**

This is an hepatoprotector. Patented in 1963.

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 – A05BA49 – R05CB12**

This is an hepatoprotector and a mucolytic. Patented in 1961

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.

**Feto-neonatal effects:** Over the years 1965-1972 (Onnis et al) there have been several reports on the use of this agent after the first trimester of pregnancy, with no adverse outcomes in offspring.

**Urazamide – A05BA49**

This agent is an hepatoprotector. 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.

**Arginine – A05BA99**

This is an amino acid. Available in Italy since 1960.

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

Studies on laboratory animals

- Naidu (1973): limbs anomalies in rats (15 mg/kg/die intraperitoneal injection)

**Citrulline – A05BA99**

Patented in 1965.

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.

**Glucometamine – A05BA99**

This is an hepatoprotector, derivative synthesis of betaine. Available in Italy since 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.

**Glucodiamine – A05BA99**

This is an hepatoprotector. 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.

**Class A05BA conclusions.** No specific studies are available in literature consistent with the use of agents of this therapeutic class in human pregnancy. In case of exposure an increase in the background reproductive risk is not likely, due to a lack of reported anomalies over the long period of commercialization and considering that teratogenic effects in laboratory animals have not been found (records provided by manufacturer for registration, not available in databases).

## **A06 – Laxatives**

Laxatives are specific drugs to help defecation. Here are the main laxative processes:

- Liquid retention in the colon and subsequent increase of feces and their softening.
- Reduction in water and NaCl absorption.
- Rise in intestinal motility with low absorption of salts and water, due to a faster transit.

### **A06AB - Contact laxatives**

Contact laxatives enable water and salt accumulation in colon and stimulate intestinal motility.

#### **Bisacodyl – A06AB02**

This is a diphenyl-methane derivative, of low absorption, considered a drug of choice by ADEC and WGZ.

#### **Castor oil – A06AB05**

This agent is a derivative from the seeds of the “Ricinus communis” (castor-oil plant), a surface-active laxative increasing water and salt secretion in intestines, by hydrating and softening the feces. The stimulation determines uterine contractions.

#### **Senna glucoside– A06AB06**

ADEC and WGZ consider it a drug of choice.

#### **Cascara – A06AB07**

ADEC and WGZ consider it a drug of choice.

### **A06AC – Bulk-forming laxatives**

These laxatives have few side effects and even fewer systemic effects. (Ispaghula – A06AC01; Sterculia – A06AC03; Polycarbohil – A06AC08).

### **A06AD – Osmotic laxatives**

Saline laxatives (Magnesium salts; Sodium phosphate) are barely absorbed (20%). They can determine Mg absorption possibly developing toxicity.

Osmotic laxatives are not absorbed (Lactulose – A06AD11; Lactitole – A06AD12; Macrogol – A06AD15).

## **A07 – Antidiarrheal, anti-inflammatory drugs and intestinal antimicrobial agents**

### **A07AA – Antibiotics**

#### **Nystatin – A07AA02**

This antimycotic agent is obtained from *Streptomyces noursei*. Barely absorbed per os and by intact mucosa and cutis. Usually used by vaginal way. Patented in 1957.

## **Retrospective cohort studies without controls**

- Culberston (1874): 25 healthy exposed newborns (the period of exposure is not specified).
- Wallenburg and Wladimiroff (1976): 49 healthy exposed newborns (the period of exposure is not specified).
- McNellis et al (1977): 53 third trimester exposures and 191 exposures over the following trimesters. There was no increase in intrauterine or neonatal deaths.

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

- Jick et al (1981), Seattle GHT: of 225 first trimester exposures, 5 newborns had congenital anomalies. Of 6,837 controls, 80 newborns had congenital anomalies. RR = 2.0 (CI 95%: 0.8-4.8).
- Aselton et al (1985), Seattle GHT: of 176 third trimester exposures, 3 newborns had congenital anomalies. Of 6,509 controls, 105 newborns had congenital anomalies. RR = 1.1 (CI 95%: 0.3-3.3).
- Rosa (1993), Michigan MSS: of 489 first trimester exposures, 20 newborns had major defects whereas 21 are expected: RR = 0.9 (CI 95%: 0.7-2.7)

**Conclusions:** The available studies on first trimester exposures do not show any increase in the population background risk. ADEC, FASS and WGZ consider it a drug of choice. CDCs (1988) recommend, if required, the use of nystatin by vaginal way during all trimesters of pregnancy.

#### **Paromomycin – A07AA06**

This aminoglycoside antibiotic is produced after *Streptomyces krestomyceticus*, chemically similar to neomycin. Barely absorbed per os and excreted as it is in feces. The potential ototoxicity of other aminoglycoside has not been proved in paromomycin. Patented in 1959.

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.

#### **Case report**

- Kreutner et al (1981): 2 exposed healthy newborns in 13<sup>th</sup> and 23<sup>rd</sup> week.

#### **Amphotericin B – A07AA07**

It is an antimycotic, not absorbed by intestinal tract. Patented in 1956.

#### **Case report**

- Curole (1981); Harris (1966); Hadsall and Acquarelli (1973); Peterson et al (1989); Chotmongkol and Siricharoensang (1911); Pereira et al (1993): 7 healthy newborns exposed in the first trimester.
- Cohen (1987): 1 newborn with microcephaly and pilonidal sinus exposed in the third trimester.

#### **Cohort prospective studies with internal controls**

- Heinonen et al (1977); CPP: 9 healthy newborns exposed during the early 16 weeks.

Feto-natal effects: several 2<sup>nd</sup> and 3<sup>rd</sup> trimester exposures have been reported, but no adverse effect on the newborn has been recorded. (Feldman 1959, Littman 1959, Winn 1959, Philpot and Lo 1972, Aitken and Symonds, 1962, Kuo 1962, Mick et al 1972, Silberfarb et al 1972, McCoy et al 1980, Curole 1981, Smale and Waechter 1970, Hadsal and Acquarelli, 1973, Neiberg et al 1977, Ismail and Lerner 1982, McGregor et al 1986, Cohen 1987, Hager et al 1988, MacDonald and Arguire, 1990, Pereira et al 1993, Thakir et al 1993, Dean et al 1994, Mareshwari

et al 1994, Shalev et al 1994, Gradoni et al 1994, Chen and Wang 1996, Trivedi et al 2002).

**Conclusions:** The available studies on first trimester exposures to amphotericin do not establish any increase in the population background risk. Its use in other periods of pregnancy has, least of all, not revealed any harmful effects to the newborns. Amphotericin is the sole drug approved for treating blastomycosis in pregnancy. (Chapman et al., 2000).

#### **Vancomycin – A07AA09**

This is a glycopeptide antibiotic. Barely absorbed per os. It is potentially ototoxic. Patented in 1962.

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

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

- Byrd et al (1994: nonteratogenic either in rats (200 mg/kg) or in rabbits.

**Feto-neonatal effects:** Following exposures during the second and third trimesters of pregnancy neither neurosensorial deafness, nor nephrotoxicity have been reported.

#### **Colistin (Polymyxin E) – A07AA10**

Polypeptide antibiotic obtained after *Aerobacillus colistinus*. Its oral absorption is poor, but a modest absorption may occur in case of lesions of the intestinal mucosa. Patented in 1966.

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

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

- Saitoh et al (1981): nonteratogenic in mice (500 mg/kg e.v.).
- Tsujiani et al (1981): nonteratogenic in rabbits (80 mg/kg).
- Tsujiani et al (1981): nonteratogenic in rats (25 mg/kg)
- Tomizawa and Kamada (1973): nonteratogenic either in mice (150 mg/kg) or in rats (40 mg/kg).

#### **Rifaximin – A07AA11**

It is an antibiotic, semisynthetic derivative of rifamycin. Its intestinal absorption is poor, less than 1%. 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.

#### **Bacitracin – A07AA51**

This antibiotic is obtained from filtrated cultures of *Bacillus subtilis*. Its intestinal absorption is poor (3%). Patented in 1949.

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

- Heinonen et al (1977), CPP: of the 18 newborns exposed during the early 16 weeks, they were healthy babies.

#### **Neomicine – A07AA51**

It is an antibiotic and aminoglycoside, barely absorbed per os. Potentially ototoxic, although such a potential has not been assessed in fetuses as it has, instead, occurred in the case of other aminoglycosides. Patented in 1950.

**Case-control studies, nonspecific**

- Czeizel et al (2000), Hungarian CCSSCA: 22,865 case newborns showing congenital anomalies, 38,151 healthy controls. 12 among the cases and 14 among the controls had been exposed: OR 0 1.4 (CI 95%: 0.7-3.1)

**Prospective cohort studies with internal controls**

- Heinonen et al (1977), CPP: of 30 exposed newborns in the early 16 weeks, they were all healthy babies.

**A07AA class conclusions:** Some antibiotics of this therapeutic class have been fully studied (nystatin, amphotericin and neomycin) but there are no available specific studies on their use in pregnancy. Concerning other agents, instead, and in some cases the studies are limited. In case of exposure an increase in the population background reproductive risk is not likely, due to a lack of reported anomalies over the long period of commercialization and considering the chemical characteristics of the agent. Besides, teratogenic effects in laboratory animals have not been found (records provided by manufacturer for registration, not available in databases).

## **A07AC – IMIDAZOLE DERIVATIVES**

### **Miconazole – A07AC01 – G01AF04 – J02AB01**

This is an antimycotic, imidazole derivative. Its intestinal and vaginal absorption is poor. Patented in 1969.

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

- Culberston (1974): 33 healthy newborns, exposed by vaginal way. The period of exposure is not specified.
- Rutherford (1976): 40 exposures by vaginal way. No adverse effect in mothers or newborns (exposure period not specified).
- Wallenburg and Wladimiroff (1976): 49 healthy exposures by vaginal way (exposure period not specified)
- Mc Nellis et al (1977): 43 first trimester exposures by vaginal way, and 248 systemic exposures in the second half of pregnancy. No increasing incidence in congenital anomalies.
- Weisberg (1986): 471 exposures in not specified periods of pregnancy with any adverse effects in mothers or newborns.

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

- Jick et al (1981), Seattle GHC: of 360 first trimester exposures, 1 newborn had congenital anomalies. Of 6,837 controls, 80 newborns had congenital anomalies. RR = 2.0 (CI 95%: 0.03-1.6).
- Rosa (1993), Michigan MSS: of 7,266 first trimester exposures by vaginal way, 304 newborns had major defects, 273 expected. RR = 1.1 (CI 95%: 0.9-1.3).

**Conclusions:** Available studies on miconazole exposure in the first trimester of gestation do not assess any increase in the population background reproductive risk.

## **A07AX – Other intestinal antibiotics**

### **Nifuroxazide – A07AX03**

This intestinal antiseptic is a synthetic nitrofurantoin derivative. Barely absorbed per os. Patented in 1962.

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 is no written evidence of specific studies concerning the use of nifuroxazide in human pregnancies. In case of exposure an increase in the population background reproductive risk is not likely, due to a lack of reported anomalies over the long period of commercialization and the absence of teratogenic effects in laboratory animals (records provided by manufacturer for registration, not available in databases).

## **A07B - Intestinal adsorbents**

### **Coal – A07BA01**

### **Diosmectide – A07BC05**

### **Kaolin – A07BC30**

## **Attapulgite – A07BC54**

**Conclusions:** These are agents lacking systemic absorption. There are no written specific studies concerning their use in human pregnancy. An increase in the population background reproductive risk is not likely. This in consideration of their chemical characteristics and due to a lack of reported anomalies over the long period of commercialization.

## **A07DA – Antipropulsives**

### **Loperamide – A07DA03**

This is an antidiarrheal and antipropulsive agent, opioid (opium alkaloid) and synthetic piperidine derivative. Patented in 1970.

#### **Cohort retrospective studies with internal controls**

- Rosa (1993), Michigan MSS: of 108 first trimester exposures, 6 newborns appeared with major defects, 5 expected (RR = 1.2; CI 95%: 0.4-2.6), 3 of them with cardiopathy (1 expected) (RR = 3.0; CI 95%: 0.6-8.7).

#### **Cohort prospective studies with internal controls**

- Einarson et al (2000), cooperative study of 5 TIS: 89 first trimester exposures and as many controls. No increase of congenital anomalies in offspring.

**Conclusions:** The available studies, although limited, do not suggest any association of loperamide and population background reproductive risk. The risk is not even conjecturable, considering the lack of reported anomalies over the long period of commercialization and due to the absence of teratogenic action on laboratory animals (records provided by manufacturer for registration, not available in databases).

## **A07E – Intestinal anti-inflammatory drugs**

### **A07EB – Antiallergic drugs**

#### **Cromoglycic acid – A07EB01 – R03BC01**

This antiasthmatic and antiallergic drug is barely absorbed in the intestinal tract and it is ionized at physiologic pH. It therefore does not cross most of biologic membranes. In fact, less than 1% of the intake is absorbed. Inhalation is used to prevent asthma but when this drug is inhaled it is barely absorbed and does not cause undesired outcomes in the fetus (Walker et al 1971, Dykes 1974, and Wilson 1982). Patented in 1965.

#### **Case report**

- Hernandez et al (1980), Serembe and D'Elia (1972): 4 newborns exposed throughout pregnancy.

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

- Wilson (1982): of 296 inhalation exposures, 4 newborns had congenital anomalies (1.35%).
- Fisons Corporation (1983), quoted by Briggs et al 2002: of 185 inhalation exposures, 7 newborns had congenital anomalies and 3 of them were of genetic origin (3.8%).

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

- Rosa (1993), Michigan MSS: of 191 first trimester exposures, 7 newborns had major defects, 8 expected. (RR = 0.9; CI 95%: 0.4-1.8)

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

- Schatz et al (1977): The study cohort included 824 newborns of asthmatic mothers, whereas the control cohort included 678 newborns of non-asthmatic mothers; mothers of both cohorts were interviewed about drug intake before the 28<sup>th</sup> week of gestation. Data were analyzed considering the group of drugs used to treat maternal asthma. Matching was done between subjects exposed to a specific drug vs. non-exposed to that same drug, but possibly exposed to another antiasthmatic drug. Findings revealed that of 151 first trimester exposures to cromolyn, 9 had non-specified malformations. Whereas of 1,348 newborns not exposed to the drug, 67 had malformations (RR = 1.2; CI 95%: 0.6-2.4).

**Conclusions:** The available studies and the poor systemic absorption do not suggest a possible increase in the population background reproductive risk. Besides, there is a lack of reported anomalies over the long period of commercialization as well as of teratogenic action on laboratory animals (records provided by manufacturer for registration, not available in databases).

### **A07EC – Aminosalicylic acid and its analogs**

Some salicylates are used for their local effects to treat intestinal inflammatory diseases.

#### **Sulfasalazine – A07EC01**

This is a drug made up of a sulphamide component (sulfapyridine) and a molecule of 5-aminosalicylic acid (5-ASA). In the colon lumen sulfasalazine is cleaved into 2 main metabolites: sulfapyridine and 5-aminosalicylic acid. Sulfapyridine reveals a certain tendency to accumulation and it completely disappears from the serum 3 days after it has been interrupted. 5-ASA agent is absorbed in limited quantities. The drug crosses the placenta and concentrations appearing in the umbilical cord are about half those in the maternal serum. 5-ASA levels are very low both in the maternal serum and in the cord. Sulfapyridine, like other sulphamides, can determine a higher probability of kernicterus, when administered late in pregnancy. This, in spite of the study by Jarnerot et al (1981), assessing concentration of sulfasalazine and sulfapyridine in the fetus not to be determining in significantly removing bilirubin from albumin. Sulfapyridine might therefore be administered in pregnancy until delivery, with no risks for the baby at term. Patients with 6-phosphate glucose dehydrogenase should be kept under close surveillance to detect, if the case, evidence of hemolytic anemia. Oligospermia and infertility have been described in men treated with sulfasalazine: its effects have been proved reversible when the drug was suspended. Patented in 1946.

#### **Case report**

Craxi and Pagliarello (1980): 1 newborn with hydrocephaly and bilateral labio cleft palate exposed throughout pregnancy.

Newman and Correy (1983): 1 newborn with cardiopathy (coarctation of the aorta + DIV) and 2 stillbirths (twins, one affected by polycystic kidney, the other showing bilateral renal agenesis, hypoplastic lung and clubfoot), exposed since conception.

Zwi and Becroft (1986): 1 fetus of 26 weeks with hydrops and aplastic anemia exposed to prednisone and sulfasalazine up to the second month of pregnancy, and, later, to prednisone alone.

Hoo et al (1988): 1 macrocephalous newborn with cardiopathy (coarctation of the aorta + DIV) exposed throughout pregnancy. Another newborn to a previous pregnancy exposed since the 4<sup>th</sup> month did not show any congenital anomalies.

Koyama et al (1966): 1 first trimester exposure had holoprosencephaly, LPS and hypotelorism. The newborn had undergone ovarian stimulation with gonadotropin.

Ishijma et al (1999): 1 healthy newborn had been exposed to corticosteroids, sulfasalazine, ceftazidim and parental nutrition in the second trimester of pregnancy

### **Cohort studies without controls**

Levy et al (1981): 60 pregnancies of 31 women suffering from ulcerative colitis. 7 of them had been treated with sulfasalazine, 5 with steroids, and 2 with azathioprine: none of the newborns presented congenital anomalies.

Baiocco and Korelitz (1984): 147 pregnancies of women suffering from Crohn syndrome and ulcerative colitis. Of 34 exposures to sulfasalazine alone or in association with steroids, 2 newborns presented clubfoot.

Nielsen et al (1984): 109 pregnancies of 68 women suffering from Crohn syndrome, 31 of which exposed to sulfasalazine (see below). 76 newborns had no congenital anomalies, whereas one stillbirth presented multiple defects (it is not specified if the fetus had been exposed). The dosage and the exposure period are not specified.

|                                 | Pregnancies | Spontaneous Abortions | VIP | Baby at term | Premature birth | Stillbirth |
|---------------------------------|-------------|-----------------------|-----|--------------|-----------------|------------|
| No drugs                        | 63          | 3                     | 9   | 43           | 7               | 1          |
| Sulfasalazine                   | 24          | 4                     | 4   | 12           | 3               | 1          |
| Corticosteroids                 | 15          | 0                     | 6   | 3            | 4               | 2          |
| Sulfasalazine + Corticosteroids | 7           | 3                     | 0   | 3            | 1               | 0          |
| Total                           | 109         | 10                    | 19  | 61           | 15              | 4          |

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

Norgard et al (2001), Hungarian CCSCA: 22,865 cases with congenital anomalies, 38,151 controls with no congenital anomalies. 17 exposures among cases, vs. 26 controls (OR = 1.2; CI 95%: 0.6-2.1)

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

Mogadan et al (1980-1981): a cohort of women suffering from Crohn syndrome or ulcerative colitis was exposed for most of the first trimester. 102 exposures to sulfasalazine had no congenital anomalies; 84 also exposed to steroids produced 2 newborns with congenital anomalies (cardiopathy, cleft palate and microglossia). Of 245 not exposed to drugs, only one newborn presented a congenital anomaly (spina bifida). There was no increase in the reproductive risk concerning other outcomes, such as spontaneous abortion, prematurity, low prenatal weight.

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

Nielsen et al (1983): 135 newborns from 173 pregnancies of 97 women suffering from ulcerative colitis, exposed to sulfasalazine and to a combination of sulfasalazine and corticosteroids. No increase in malformation rate for prematurity or neonatal hyperbilirubinemia.

**Conclusions:** An association of first trimester exposures to sulfasalazine and some defects, with no analogies between each other, reported in some surveys

have not found any confirmation in other far-ranging studies. ADEC, FASS and WGZ consider it a drug of choice.

### **Mesalazine (5-aminosalicylic acid – 5 ASA) – A07EC02**

pH7 soluble enteric-coated tablets, are administered in order to release the therapeutic principle in the ileal more distal tract and in the colon. The agent does not appear to be well absorbed by colon and it is excreted with feces, unaltered. The absorbed amount is instead soon excreted with urine. Only a minimal amount crosses the placenta. The suspension for rectal administration releases mesalazine in the end tract of intestine (ma non c'è altro modo di dirlo, in italiano?). Suspensions reveal a very little systemic absorption, equal to about 10% of the administered dose in subjects with inflammatory bowel disease. Patented in 1940.

### **Case report**

- Colombel et al (1994): 1 newborn with renal failure (due to tubulointerstitial lesion, exposed since the 4<sup>th</sup> month of pregnancy).

### **Cohort studies without controls**

- Habal et al (1933): 18 healthy newborns exposed throughout pregnancy
- Marteau and Devaus (1994), manufacturer: 60 exposures during pregnancy. No neonatal nephrotoxicity was found.
- Trallori et al (1994): 19 exposures during pregnancy. There were no adverse effects on newborns.
- Jonville-Bera et al (1994): of 11 exposures at different moments of pregnancy, 9 healthy newborns and 1 with congenital anomalies not exposed during the first trimester.
- Bell and Habal (1997): 19 healthy newborns exposed throughout pregnancy.
- Marteau et al (1998), manufacturer: of 126 exposed newborns, 96 of whom in the first trimester, 5 newborns (5.2%) presented congenital anomalies (hyperoxalemia, cataract, pyloric stenosis in 2 twins, and dislocation of the hip).
- Ludvigsson and Ludvigsson (2002): during a survey made for other purposes, 14 newborns have been reported exposed to mesalazine and 4 more to sulfasalazine with no adverse effects.

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

- Diav-Citrin et al (1998), TIS Motherisk Program: in a cohort study of 127 women exposed during the first trimester, 1 newborn had congenital anomalies; of 131 not exposed women of the control group, 5 newborns presented congenital anomalies. (RR for major defects = 0.2; CI 95%: 0.0-1.7, whereas RR for mild defects = 1.7; CI 95%: 0.6-4.9).
- Norgard et al (2003, PEP Database North Jutland: in a cohort study 60 women were exposed either during the first trimester, or one month before pregnancy. The control group included 19,418 not exposed pregnancies. OR for congenital anomalies = 1.9 (CI 95%: 0.7-5.4); for stillbirth rate = 6.4 (CI 95%: 1.7-24.9) for prematurity = 1.9 (CI 95%: 0.9-3.9); for low neonatal weight = 1.2 (CI 95%: 0.4-3.3).

**Neonatal effects:** The percentage of regular pregnancy outcomes is the same both in women undergoing an intestinal anti-inflammatory therapy (mesalazine, olsalazine and azathioprine) and women who had interrupted it (Tennenbaum et al 1999). The hypothesis of association between intake of the agent in the second half of pregnancy and renal failure (Colombel 1994) has not been confirmed.

### **Olsalazine – A07EC03**

This agent is made up of two molecules of 5-aminosalicylic acid (5-ASA) combined by nitrogen bond. It is a relatively inert compound and its intestinal absorption is very low. 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.

### **Balsalazide – A07EC04**

This agent is made up of mesalazine combined by azoic bond to the inert molecule-vehicle 4-aminobenzoil- $\beta$ -alanine. Systemic absorption is very poor (<1%), most of the dose decays in colon due to bacterial azo-reductase, producing 5-ASA and 4-aminobenzoil- $\beta$ -alanine (4-ABA). Available in Italy since 2001.

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.

**A07EC class conclusions:** Mesalazine has been sufficiently studied. There is no written evidence of association between 5- ASA and either its analogs or population background reproductive risk.

## **A08AA – Central-action drugs against obesity**

### **Subutramine – A08AA10**

This drug inhibits reuptake of serotonin, noradrenalin and dopamine. It is available in Italy since 2001.

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.

## **A08AB – Peripheral-action drugs against obesity**

### **Orlistat – A08AB01**

This intestinal lipase inhibitor is so poorly absorbed that it is not possible to measure plasma concentration (<5ng/ml) 8 hours after its administration. Available in Italy since 1999.

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.

**A08AA and A08AB class conclusions:** There is no written evidence of specific studies concerning the use of this drug in human pregnancy. In case of exposure an increase in the population background reproductive risk is not likely, since its systemic absorption is non-existent and there are not reported anomalies over the long period of commercialization (records provided by manufacturer for registration, not available in databases).

## **A09 – Digestants**

### **A09AA – Enzymes**

#### **Pancrelipase – A09AA02**

This is a digestive enzyme derived from swine pancreas. 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.

#### **Pancreatin – A09AA02**

This is a digestive enzyme derived from swine and bovine pancreas. It is not absorbed by intestine and it appears not to cross placenta. Available in Italy since 1969.

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

- Heinonen et al (1977), CPP: 3 exposures in the early 16 weeks, all healthy newborns.

#### **Tilactase – A09AA04**

This digestive enzyme transforms lactose into glucose and galactose. Available in Italy since 1989.

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.

#### **Lysozyme – A09AA49**

This is a polypeptide enzyme usually existing in the body. It is one of the factors of aspecific cellular and humoral immunity. Available in Italy since 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.

**A09AA class conclusions:** There is no written evidence of specific studies concerning the use of drugs of this therapeutic class in human pregnancy. In case of exposure an increase in the population background reproductive risk is not likely, due to a lack of both reported anomalies over the long period of commercialization and teratogenic action on laboratory animals (records provided by manufacturer for registration, not available in databases).

### **A09AB – Acid-based preparations**

#### **Betaine – A09AB02**

This digestant being a quaternary ammonium compound it scarcely crosses the placenta. Patented in 1928.

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 is no written evidence of specific studies concerning the use of drugs of this therapeutic class in human pregnancy. In case of exposure an increase in the population background reproductive risk is not likely, due to a lack of both reported anomalies over the long period of commercialization and teratogenic action on laboratory animals (records provided by manufacturer for registration, not available in databases).

## **A 10 - Drugs used against diabetes**

Children of diabetic mothers show an increase in incidence risk of congenital anomalies, 3-5 times higher than the rest of the population (American College Obstetricians Gynecologists 1994, Tower et al 1995). This incidence is related to glycemic control in the first trimester. There is no risk increase in offspring of mothers suffering from gestational diabetes not insulin-dependent (Becerra et al 1990). There are defects which can be attributable to poor glycemic control, such as cardiopathies (TGV, DIA, DIV) (2%), caudal regression sequence (0.2-1%), situs viscerum inversus (0.05-0.1%), double urethra (0.05-0.1%), renal agenesis (0.01-0.02%), anencephaly (0.01-0.02%) and holoprosencephaly (0.01-0.02%) (Mills 1982, American College Obstetricians Gynecologists 1994).

**Feto-neonatal effects:** the following should be attributable to poor glycemic control. Perinatal mortality 4.6% vs. 2.4 among population in general; perinatal morbidity 65% (hypoglycemia, hyperbilirubinemia, hypocalcemia and polycythemia) (Gabbe et al 1977).

### **A10A – Insulin and analogs**

#### **Insulin – A10A**

This is an anti-diabetic agent, a peptic pancreatic hormone. It does not cross the placenta. Risk of congenital major defects in offspring of diabetic mothers insulin-dependents: RR 0 7.9 (CI 95%: 1.9-33.5) (Becerra et al 1990), OR = 8.7 (CI 95%: 1.8-34.7) (Ramos – Arroyo 1992). The risk increase is evidently attributable to the disease and not to insulin.

**Conclusions:** Insulin is a drug of choice to control diabetes in pregnancy. Diabetic embryopathy is avoidable with an adequate glycemic control (Reece et al 1996; see chapter on pre-conception advice).

### **A10B – Oral hypoglycemics**

Oral hypoglycemics are used to treat diabetes of type 2 in case this cannot be restrained by a diet and by an increase physical activity. They control glycemia (although not as well as insulin) and improve peripheral use of glucose (Biguanides) or else they stimulate insulin secretion (Sulfonamides).

#### **Case-control**

- Harris (1971): 3 exposures to non-specified oral hypoglycemics caused 1 clubfoot and 2 multiple non-specified malformations.

#### **Retrospective cohort studies without controls**

- Coetzee and Jackson (1984): In the cohort study 78 women were treated with chlorpropamide and metformin during the first trimester. 2 newborns had major defects. 93 women of the control study suffering from diabetes were not exposed. Perinatal mortality (4.0%) was higher among exposed to high doses in the first trimester, due to inadequate glycemic control late in pregnancy.
- Coetzee and Jackson (1985): 691 pregnant women were exposed to metformin or glibenclamide. 423 of them had gestational diabetes, 268 instead were diabetics before pregnancy; 80 pregnant women suffering from diabetes were treated with dietary restrictions. An increase in the incidence of congenital anomalies has not been noticed in the offspring exposed to metformin and glibenclamide vs. the rest of the population. Perinatal mortality

in gestational diabetes: 14/1000, in pre-pregnancy diabetes: 57/1000 and in non-treated diabetes 313/1000.

- Hellmuth et al (1994): 25 healthy newborns exposed in the first trimester to oral hypoglycemic drugs due to maternal type 2 diabetes. There were no newborns with major congenital defects, 1 newborn had a mild congenital defect.

**Retrospective cohort studies with internal controls**

- Botta (1997): 362 women with ID diabetes, 130 women with non-ID diabetes. The percentage of congenital anomalies in newborns from diabetic non-ID mothers treated with oral anti-diabetics was of 11.6% vs. 1.4% among newborns from non-treated non-ID diabetic mothers (p<0.01).

**Prospective cohort studies with internal controls**

- Piacquadio et al (1991): Study cohort: 20 women suffering from non-insulin dependent diabetes treated from week 3 to the 28<sup>th</sup> week with different oral hypoglycemics (16 sulfonylureas, 1 metformin, 2 phenformin and 1 unknown); control cohort: 40 women with non-insulin dependent diabetes matched per age, race, parity and glycemic control. In the study cohort 16 newborns had major or mild defects (see below); in the control cohort 36 newborns had congenital anomalies (RR for congenital anomalies = 4.1; CI 95%: 1.8-9.2).

| Antidiabetic   | Exposure Week    | Congenital anomaly   |
|----------------|------------------|--|
| Unknown        | 3 <sup>rd</sup>  | Hydrocele sn   |
| Chlorpropamide | 22 <sup>nd</sup> | Microtia, preauricular appendix  |
| Chlorpropamide | 8 <sup>th</sup>  | Preauricular appendix  |
| Chlorpropamide | 14 <sup>th</sup> | Single umbilical artery  |
| Phenformin     | 15 <sup>th</sup> | DIA  |
| Tolazamide     | 12 <sup>th</sup> | Auricular defect   |
| Glyburide      | 10 <sup>th</sup> | Anencephaly  |
| Chlorpropamide | 10 <sup>th</sup> | Preauricular appendix  |
| Chlorpropamide | 15 <sup>th</sup> | Facial, auricular and vertebral Abnormalities, DIV                     |
| Glyburide      | 23 <sup>rd</sup> | Vertebral anomalies, DIV   |
| Chlorpropamide | 14 <sup>th</sup> | Vertebral anomalies, DIV, aortic coarctation and preauricular appendix |

- Towner et al 1995: 332 newborns from diabetics treated since the first trimester. 125 of them had been controlled with a diet, 147 treated with oral hypoglycemics (mainly chlorpropamide, glibenclamide, or glipizide), 60 more of them had been administered insulin. 56 (16.9%) newborns had congenital anomalies; 39 (11.7%) had major defects; 17 (5.1%) had mild defects.

| Treatment              | Major defects | Mild defects |
|------------------------|---------------|--------------|
| Diet (125)             | 18 (14.4%)    | 6 (4.8%)     |
| Hypoglycemics os (147) | 14 (9.5%)     | 9 (6.1%)     |
| Insulin (60)           | 7 (11.7%)     | 2 (3.3%)     |
| Total (332)            | 39 (11.7%)    | 17 (5.1%)    |

**Feto-neonatal effects:** there was no difference as per neonatal mortality between exposures to oral hypoglycemics and exposures to insulin; there were not severe cases of neonatal hypoglycemia or icterus among exposures to oral anti-diabetics (Hellmuth et al 2000). Perinatal mortality among newborns

exposed to metformin in the third trimester was of 11.6% vs. 1.3% among non-exposed ( $p < 0.02$ ) (Hellmuth et al 2000).

### **A10BA – Biguanides**

These drugs control glycemia improving the peripheral use of glucose. They inhibit hepatic gluconeogenesis and reduce intestinal absorption of glucose.

#### **Metformin – A10BA02**

This is used also in the treatment of polycystic ovary disease. Patented in 1995.

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

- Gluek et al (2001,2002 a,b): 72 women suffering from polycystic ovary disease were treated with metformin. 28 of them were treated throughout pregnancy. 84 fetuses were exposed at periconception: 14 resulted in spontaneous abortion (17%), 63 were born without congenital anomalies, 7 more pregnancies are being surveyed and at the moment there are no congenital anomalies visible to echography.

**Feto-neonatal effects:** preeclampsia increase in diabetic women treated with metformin vs. diabetic women treated with sulphonylurea and insulin (10%  $p < 0.02$ ); perinatal mortality increase in third trimester exposures to metformin vs. exposures to sulphonylurea or insulin ( $p < 2.2$ ) (Hellmuth et al 2000); hyperbilirubinemia (30%), macrosomia (18%) (Coetzee and Jackson 1985).

#### **Phenformin – A10BD01**

It is available in Italy in association with glibenclamide or chlpropamide, since 1962.

### **A10BB – Sulphonamides, urea derivatives**

These drugs control glycemia stimulating insulin secretion and increasing cell receptors for insulin. Besides, they reduce tissue resistance to insulin hence increasing its receptor affinity.

#### **Glibenclamide (Glyburide) – A10BB01**

This is a second-generation sulphonylurea, structurally similar to glipizide. Placental transfer of glyburide is minimal due to its high degree of protein binding; besides, it appears to have short half-life (Elliot et al 1991). Patented in 1965.

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

- Rosa, (1993), Michigan, MSS: of 37 first trimester exposures 1 newborn had major defects, 2 expected: RR = 0.5 (CI 95%: 0.0-2.8).

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

- Langer et al (2000): 203 women with gestational diabetes were treated with insulin vs. 201 treated with glibenclamide. There was no difference between the two groups either in the percentage of major congenital anomalies (2%), or in the neonatal complications.

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| Langer et al 2000    | Glibenclamide (201) | Insulin (203)   |
|----------------------|---------------------|-----------------|
| Congenital anomalies | 5 (2%)              | 4 (2%)          |
| Macrosomia           | 14 (7%)             | 9 (4%)          |
| Hypoglycemia         | 18 (9%)             | 12 (6%)         |
| Hyperbilirubinemia   | 12 (6%)             | 8(4%) Pulmonary |
| complications        | 16 (8%)             | 12 (6%)         |

|                 |          |          |
|-----------------|----------|----------|
| Stillbirths     | 1 (0.5%) | 1 (0.5%) |
| Neonatal deaths | 1 (0.5%) | 1 (0.5%) |

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**Feto-neonatal effects:** hypoglycemia in third trimester exposures (Coetzee and Jackson 1980)

### **Chlorpropamide – A10BB02**

This is a first-generation sulphonylurea. Patented in 1961.

#### **Case report**

- Campbell (1963): 1 first trimester exposure showing microcephaly and spastic quadriplegia.
- Assemany et al (1972): 1 exposure showing caudal dysplasia
- Soler et al (1976): 3 first trimester exposures with: hand and digit anomalies, ileal stenosis, death and preauricular sinuses.

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

- Rosa (1993) Michigan MSS: 18 first trimester exposures, no newborns with congenital anomalies, 1 expected.

**Feto-neonatal effects:** neonatal hypoglycemia (Zucker and Simon 1968, Kemball et al 1970, Harris 1971, Friend 1981, Piacquadio et al 1991), hyperbilirubinemia, polycythemia and hyperviscosity (Piacquadio et al 1991).

### **Glipizide – A10BB07**

This is a second-generation sulphonylurea, structurally similar to glibenclamide. Available in Italy since 1994.

**Feto-neonatal effects:** neonatal hypoglycemia due to pre-birth exposure (Shuman 1983).

### **Gliquidone – A10BB08**

It is a second-generation sulphonylurea, available in Italy since 1985.

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

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

- Iida et al (1976): it appears to be nonteratogenic in rats or in rabbits

### **Gliclazide – A10BB09**

This is a second-generation sulphonylurea. Patented in 1966.

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

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

- Kawanishi et al (1981): it appears to be nonteratogenic in rats or in rabbits

### **Glimepyride – A10BB12**

This is a second-generation sulphonylurea. Available in Italy since 1996.

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

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

- Baeder et al (1993): anophthalmia was noticed in rats, while skeletal anomalies and anomalies of the abdominal wall and of the eyes, attributable to maternal hypoglycemia, were evident in rabbits.

#### **Gliciclamide – A10BB49**

This is a first-generation sulphonylurea, available in Italy since 1995.

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.

#### **Glisolamide – A10BB49**

This is a second-generation sulphonylurea, available in Italy since 1980.

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.

**A10BA and A10BB class conclusions:** There is no written evidence of an association between either biguanides or sulphonamides and an increase in the population background reproductive risk. The increase of congenital anomalies reported in some studies should be attributed to poor glycemic control of diabetes due to the use of oral hypoglycemic agents. Oral anti-diabetic drugs are not recommended in pregnancy, due to their potentiality to cause both fetal hyperinsulinemia and hypoglycemia. In case of exposure, a risk increase is not likely, at least not specifically connected with the drug. This, in consideration of the available studies on some agents and the lack of teratogenic effects on laboratory animals (records provided by manufacturer for registration, not available in databases). Recent studies suggest the idea that glibenclamide is to be considered an alternative to insulin for the treatment of gestational diabetes (Langer 2002).

#### **A10BF – Alpha-glucosidase inhibitors**

##### **Acarbose – A10BF01**

This complex oligosaccharide inhibits the action of pancreatic amylase and of intestinal alpha-glucoside hydrolase. This inhibition results in delayed absorption of ingested carbohydrates. Less than 2% of the oral dose is absorbed in intestine, but systemic absorption of metabolites is of 30%. Available in Italy since 1994.

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

- Wilton et al (1998): 5 first trimester exposures caused 2 spontaneous abortions, but 3 were healthy newborns.

**Conclusions:** There is no written evidence of specific studies concerning the use of acarbose in human pregnancy. In case of exposure an increase in the population background reproductive risk is not likely, considering its pharmacological characteristics and due to a lack of both reported anomalies over the long period of commercialization and teratogenic action on laboratory animals (records provided by manufacturer for registration, not available in databases).

#### **A10BX – More oral hypoglycemic agents**

##### **Repaglinide – A10BX02**

It is a carbamoyl-methyl, derivative of benzoic acid. It stimulates insulin secretion and it is available in Italy since 1999.

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

### **Studies on laboratory animals**

- Viertel et al (2000): it appears to be non-teratogenic in rats. Exposures to high doses and after organogenesis cause bone anomalies.

**Conclusions:** There is no written evidence on the use of repaglinide in human pregnancy. Therefore, the sole possible assessment is based on studies on laboratory animals not showing a teratogenic action.

### **A11 – Vitamins**

Vitamins can be classified according to some general characteristics. Water-soluble vitamins (vitamin C, B1, B2, niacin, B6, folic acid and B12) tend not to accumulate in the body and it is therefore necessary a constant intake. Liposoluble vitamins (vitamin A, D, E and K) settle in the body, giving rise to possible storage toxicity. The intake over an extended period of time of larger or smaller quantities increases the risk of toxicity or deficiency respectively.

Vitamin requirements over pregnancy are slightly higher than usually. Multivitamin products are regularly prescribed to pregnant women. Vitamin deficiency or excess during pregnancy, as far as some vitamins only, can be responsible of congenital anomalies. There is no written evidence of toxicity or teratogenic effects in human pregnancy, connected with an excessive intake of vitamins E, K, C, thiamin (B1), riboflavin (B2), niacin (B3), pyridoxine (B6) and cyanocobalamin (B12).

#### **Retinol (vitamin A) – A11CA101**

This is a liposoluble vitamin having a half-life ranging from a few weeks to some months. Since 1969 its content in foods and daily requirements are expressed in mg of Retinol or "Retinol-equivalent" (RE), that is equal to 3.33 IU of vitamin A or to 6 mg of b-carotene, or else to 10 IU of beta-carotene or to 12 mg of different carotenoids. The daily requirements of vitamin A in pregnancy is of 800 µg Retinol equivalent. Beta-carotene, provitamin A, can be found in many green-leaves vegetables, carrots and meat. Beta-carotene is converted into retinol by the body. Such a conversion tend to substantially diminish when the intake of beta-carotene is augmented (Morinobu et al 1994a, 1994b). Large quantities of beta-carotene cannot therefore determine toxicity or teratogenic factors (Miller 1987).

#### **Case report**

- Pilotti and Scorta (1956): 1 exposure from 6<sup>th</sup> to 10<sup>th</sup> week to 40,000 IU/die of vitamin A and 600,000 IU/die of vitamin D caused hydronephrosis, hydroureter, lack of the urethral orifice and vesical diverticulum.
- Gal et al (1969): a high dose of vitamin A has been found in the liver of an anencephalous newborn.
- Gal et al (1972): 2 newborns exposed to a high dosage of Retinol in the first trimester presented malformations in urinary system.
- Berhardt and Dorsey (1974): 1 newborn exposed to 225,000 IU/die during the first trimester and to 50,000 IU/die for the rest of pregnancy presented bilateral hydroureter, right hydronephrosis and a duplicated left urethral opening in the vagina.
- Mounoud (1975): 1 newborn exposed to 10 ml of a vitamin-A oil solution (unknown quantity) suffered from Goldenhar syndrome.

- Averback (1976): 1 17-weeks fetus showing anencephaly had been exposed to high doses.
- Stange et al (1978): 1 newborn exposed to 150,000 IU/die during the 19<sup>th</sup> to 40<sup>th</sup> day of gestation presented microcephaly and multiple cerebral abnormalities, beside renal and bilateral suprarenal hypoplasia.
- Greelen (1979): he has collected (besides the cases of Gal et al 1972 and of Bernhardt and Dossey 1974) 1 newborn with cardiovascular defect, 1 with cleft palate, 1 with craniofacial defects and 1 with spina bifida, all exposed to high dosages in the first trimester.
- Van Lennep et al (1985): 1 partial sirenomelia following a treatment with high doses of vitamin A.
- Rosa et al (1986): besides the above mentioned cases they have collected 18 voluntary reports of possible teratogenic effects due to high dosage (18,000-150,000 IU/die), 12 showing similar defects as observed in retinoid syndrome (microtia, labio-cleft palate, SNC defects, facial dysmorphism and cardiovascular system defects). The cases had been reported after the identification of the "retinoid embryopathy" made at the beginning of the '80s.
- Lungarotti et al (1987): 1 exposure to 2,000 IU/die presented multiple malformations.
- Evans and Hockey-Dwyer (1991): 1 exposure to 25,000 IU/die presented lens duplication and hourglass-like cornea.
- Fonda and Rosenbaum (1992): 1 healthy newborn to a woman who had been administered about 10 carrots a day, in the latest 2 years and up to 6<sup>th</sup> week after latest menstruation; besides, up to 3 months before conception she had taken 25,000 IU/die vitamin A.

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

- Zuber et al (1987): 27 first trimester exposures to high dosage (25,000-150,000 IU/die) did not reveal any teratogenic association.
- Bonai et al (1955): 7 healthy newborns exposed to average dosage of 70,000 IU/die (25,000-90,000).

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

- Nelson and Forfar (1971): 175 newborns with "major malformations", 283 with "mild malformations" and 911 healthy controls. 4 first trimester exposures with congenital anomalies (1 major and 3 mild), vs. 4 exposures to low but unknown doses among 911 controls (OR = 2.0; CI 95%: 0.4-9.5).
- Martinez-Frias and Salvador (1990), ECEMC: case group of 11,293 newborns with congenital anomalies, vs. 11,193 healthy controls. The exposure has been ascertained asking a general question about drugs intake (this may have caused a bias of ascertainment in the case group). 16 cases (3 unstable hip, 2 clubfoot, 1 pre-auricular appendix, 1 facial capillary angioma, 1 half-centimeter nevus, 1 polydactyly with retrognathia, 2 depressor muscle of angle of mouth hypoplasia, 1 renal duplication with unstable hip, 1 diaphragmatic hernia, 1 LS and 1 craniotabe with epulis) and 14 controls had been exposed to >10,000 IU/die of vitamin A (OR = 1.1; CI 95%: 0.2-2.5). Analysis for doses exceeding 40,000 IU/die uncovered OR = 2.7 (IC 95%: 0.8-11.7).
- Khoury et al (1996): case group of 4,918 newborns with different congenital anomalies, vs. 3,029 healthy control. The exposure has been ascertained asking a specific question on vitamin intake, disregarding dosage information. OR for exposure to multi-vitamin preparation an vitamin A at a supposed high dosage = 0.60 (CI 95%: 0.28-1.29) for all malformations. OR for anomalies possibly caused by migration defect of neural crest cells = 0.69 (CI 95%: 0.24-1.91).
- Czeizel (1998), Hungarian CCSCA: case group of 20,830 newborns with congenital anomalies, vs. 35,727 healthy controls. 1,642 exposures to

vitamin A dosage < 10,000 IU/die among cases, vs. 3,399 exposures among controls. (OR = 0.8; CI 95%: 0.8-0.9).

**Case-controls studies, specific**

- Parkinson and Tan (1982): 12 cases showing NTD, compared to 94 healthy controls. The higher concentration of vitamin A was seen in the amniotic liquid of the newborns with NTD vs. controls.
- Werler et al (1990): 2,658 cases presented malformations similar to those caused by isotretinoin (craniofacial and cardiac), while 2,609 controls had other congenital anomalies. The quantity of absorbed vitamin A is unknown. OR for vitamin A exposure in the first lunar month = 2.5 (CI 95%: 1.0-6.2), in the second lunar month = 2.3 (CI 95%: 0.9-5.8) and in the third lunar month = 1.6 (CI 95%: 0.6-4.5).
- Shaw et al (1996): two specific studies have been reported, one on labio-cleft palate (925 cases and 871 healthy controls) and the other on congenital cardiopathies (254 cases and 561 healthy controls). Exposure was ascertained asking a specific question on vitamin intake, disregarding the dosage. OR for supposed exposures to >10,000 IU of vitamin A was of 0.6 (CI 95%: 0.2-1.5) and 0 (CI 95%: 0-2-2) respectively.
- Mills et al (1997): 548 cases showing NTD vs. 387 controls (group A) with other congenital anomalies and 573 healthy controls (group B). There was no difference as far as dosage exposures, of 8,000-25,000 IU, among the three groups.

| Vitamin A exposure  | Neural crest defects OR (CI 95%) | Total congenital defects OR (CI 95%) |
|---|----------------------------------|--------------------------------------|
| >8,000 IU/day vs. exposures to <5,000 IU/day (supplementary and dietary)  | 0.8<br>(0.2-2.6)                 | 0.8<br>(0.4-1.5)                     |
| >10,000 IU/day vs. exposures to <5,000 IU/day (supplementary and dietary) | 0.7<br>(0.3-2.0)                 | 1.1<br>(0.2-0.5)                     |

- Botto et al (2001) 126 cases with single cardiovascular defects and 679 healthy controls. OR for one of the defects setting trunk/canal (due to transposition of the great vessels) for exposure >10,000 IU/day vs. exposures < 10,000 IU/day = 9.2 (CI 95%: 4.0-21.2), based on 7 exposed cases.

**Prospective cohort studies with internal controls**

- Rothman et al (1995): 24,559 women enlisted in the cohort study at 15-20 weeks of gestation were interviewed about different items, among which possible diet and drug intake, including vitamins. 22,784 women of the analyzed cohort (92.6%) underwent interview and complete follow-up of pregnancy. Malformations were ascertained thanks to medical record (75%) and maternal interview (25%).

| Vitamin A/day | Total newborns | Neural crest defects (%) | Other defects | Total |
|---------------|----------------|--------------------------|---------------|-------|
|---------------|----------------|--------------------------|---------------|-------|

|               |        |           |           |           |
|---------------|--------|-----------|-----------|-----------|
| 0-5,000 IU    | 6,410  | 33 (0.51) | 53 (0.8)  | 86 (1.3)  |
| 5,000-10,000  | 12,688 | 59 (0.47) | 137 (1.1) | 196 (1.5) |
| 10,000-15,000 | 3,150  | 20 (0.63) | 22 (0.7)  | 42 (1.3)  |
| >15,000       | 500    | 9 (1.80)  | 6 (1.2)   | 15 (3.0)  |
| Total         | 22,748 | 121       | 218       | 339       |

The analysis was carried out considering both the dietary and supplementary ingestion of vitamin A. Using a specific model of regression, researchers have observed an increase in the incidence of congenital anomalies in general and in particular of those at least partially derived from the neural crest (cranio-facial defects, neural tube anomalies, as well as thymic defects and cardiac impairments), in association with the increase of vitamin A intake. RR for neural crest defects was = 3.5 (CI 95%: 1.7-7.3) in the exposures to over 15,000 IU of vitamin A, compared to exposures to below 5,000 IU.

- Mastroiacovo et al (1999), ENTIS: The cohort study of 311 exposures in the early 9 weeks to average dosage of 50,000 IU/day (ranging between 10,000 to 300,000 IU/day) revealed 3 newborns with congenital anomalies (lung stenosis, anal stenosis with fistula and inguinal hernia). No congenital anomalies were detected in the 120 exposures to over 50,000 IU/day. There were no significant differences as per malformations or different adverse pregnancy outcomes in comparison with a group exposed after the first trimester to high doses of vitamin A (RR = 0.28; CI 95%: 0.1-1.2) and with another group exposed to nonteratogenic agents (RR = 0.5; CI 95%: 0.1-1.8).

**Conclusions:** The available studies do not give a clear answer to the question whether a high dosage of vitamin A is teratogenic or not. Some studies suggest this possibility, but they do not find consistency in other surveys. Case reports as a whole do not identify a clear malformation pattern and the excessive number of cases reporting similar defects to retinoid embryopathy is well explained by the reference bias. Case-control studies, despite of their limited value due to different problems such as dosage definition, case definition, sample size and opportunity of exposure to really high dosages, do not suggest any teratogenic effect of vitamin A, at least for dosages around 10,000 IU. Cohort studies by Rothman et al (1995) shows various ascertainment, definition and analysis problems (see Miller et al 1998 for a complete review) but it is not confirmed in the study by Mastroiacovo et al (1999), apparently the strongest on the subject.

Of particular interest are some experimental studies. A) Studies on retinoid acids and 13-cis-tretinoine levels obtained after administration of 10,000 and 30,000 IU/day of vitamin A, not showing any teratogenic increment in plasma concentration of retinoid acids. B) Studies on animal samples, among which apes, to identify the minimum-security level (NOAEL) of a nonteratogenic effect. Such studies point out an equivalent in humans between 30,000 and 40,000 IU/day (Miller et al 1998).

To sum up: a) we cannot exclude a teratogenic effect due to hypervitaminosis A; b) if it exists this is very specific and of low extent; c) if it exists it is not biologically plausible below 30,000 IU/day of vitamin A. In practice, since high dosage of vitamin A in the population of developed countries have no therapeutic nor preventive value it is advisable for women in fertile age and for pregnant women not to take doses exceeding the recommended ones, that is maximum 8,000 IU/day. In case of excessive doses, especially over 30,000 IU/day a small increase in the reproductive risk should not be excluded. So far, anyway, it is impossible to exactly quantify and qualify such a risk. Echographies might be useful, to be done in centers of choice.

### **Vitamin D and its analogs – A11CC**

(Cholecalciferol, Ergocalciferol, Dihydrotachysterol, Alphacalcidol, Calcitriol, Cholecalciferol and Calcifediol)

This is a liposoluble vitamin. The requirements of calciferol in pregnancy are of 10 mg (400 IU of vitamin D).

#### **Case report**

- Pilotti and Scorta (1965): 1 exposure between 6 and 10 weeks to 40,000 IU/day of vitamin A and to 600,000 IU/day of vitamin D presented hydronephrosis, hydroureter, absence of urethral orifice and vesical diverticulum.
- Sadeghi-Nejad et al (1980), Marx et al (1980), Salle et al (1981), Greer et al (1984), Hoper et al (1994): 5 healthy newborns exposed to high dosages of calcitriol due to maternal hypoparathyroidism.
- Callies et al (1988): 2 healthy newborns exposed to calcitriol due to maternal hypoparathyroidism. Besides, 10 cases reported by manufacturer: 2 exposures with congenital anomalies (early closure of frontal fontanel and a stillbirth with multiple malformations).

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

- Goodenday and Gordon (1971): 27 healthy newborns exposed to over 200 times the daily-suggested dose of vitamin D.

**Conclusions:** There is no written evidence of association between vitamin D and its analogs, and the population background reproductive risk. In case of exposure an increase in the risk is not likely considering the lack of reported anomalies over the long period of commercialization. There is a hypothesis, not confirmed (Taussig 1966, Anita et al 1967, Friedman and Mills 1969, Rowe and Cooke 1969), that high dosages of vitamin D be responsible for Syndrome of Williams that today we know due to a deletion 7p11.23. Cases with Williams' phenotype but without deletion should be reconsidered today.

### **Thiamine (vitamin B1) – A11DA**

### **Pyridoxine (vitamin B6) – A11HA02**

### **Cyanocobalamin (vitamin B12) – B03BA01**

**Conclusions:** There is no written evidence of association between group B vitamins and an increase in the population background reproductive risk. Such a risk is not even likely, considering the lack of reported anomalies over the long period of commercialization and the results of studies on laboratory animals, not showing any teratogenic action.

### **Ascorbic acid (vitamin C) – A11GA01**

This vitamin is water-soluble.

#### **Case report:**

- Cochrane (1965): 2 newborns exposed to over 6 times the recommended daily dose of vitamin C.

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

- Nelson and Forfar (1971): 175 newborns with major defects and 283 with mild defects among whom 10 exposures vs. 23 out of 911 controls. OR = 0.9: CI 95%: 0.4-1.9. No increase in vitamin C use compared to the control group.

**Conclusions:** There is no written evidence of association between group B vitamins and an increase in the population background reproductive risk. Such a

risk is not even likely, considering the lack of reported anomalies over the long period of commercialization.

#### **A14 – Systemic anabolic agents**

Nandrolone – A14AB01

This is an ester derivative. When injected it is slowly absorbed and it is slowly and constantly released, so that in human its therapeutic effects last at least 3 weeks. Patented in 1995.

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

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

- Kawashima et al (1977): no change in utero-vaginal septum of female fetuses of rats, up to 10 mg per os.

**Conclusions:** No specific studies have been located in literature consistent with the use of this agent in human pregnancy. There is, theoretically, the possibility of an increased masculinization of external genitals of female fetuses due to virilizing effects of the drug, although experiments on laboratory animals do not support this theory.

#### **A16 – More drugs of gastrointestinal system and metabolism**

##### **Imiglucerase – A161B02**

This is an enzyme used as substitutive therapy to treat the disease of Gaucher. 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.

#### **Case report**

- Sherer et al (2002): 1 healthy newborn exposed all over pregnancy to imiglucerase, aspirin, heparin at low molecular weight, and prednisone.

**Conclusions:** No specific studies have been located in literature consistent with the use of this agent in human pregnancy. An increased population background reproductive risk is not likely, considering the chemical characteristics of this drug.