

C – CARDIOVASCULAR SYSTEM

C - Cardiovascular system

C01 – Cardiac Therapy

C01AA – Digit glycosides

Digitoxin – C01AA04

Digoxin – C01AA05

Methyldigoxin – C01AA08

Patented in 1930.

Retrospective cohort studies with internal controls

- Rosa (1993), Michigan MSS. Of 34 first trimester exposures, 1 newborn had major defects, 1 expected (RR = 1.0; CI 95% 0.0-5.6).
- Heinonen et al /1977), CPP. Of 52 early 16 weeks exposures, 2 newborns with congenital anomalies (ARR = 0.8; CI 95%: 0.2-3.3).

Feto-neonatal effects: there are many case-reports on the use of digit drugs at any stage of pregnancy, to treat circulatory pathologies of both the mother and the fetus, with no adverse effects on either subject (Briggs et al 2002). 1 fetal death has been reported in a study on maternal overdose at the 8th month of pregnancy (Sherman and Locke 1960).

C01AA class conclusions: There is no written evidence of any association between digit glycosides and increased risk. In case of exposure an increase in the background reproductive risk is not even 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). ADEC, FASS and WGZ consider digoxin a drug of choice in pregnancy.

C01B – Antiarrhythmic drugs

Quinidine – C01BA01

This drug, when administered at high dosages, has oxytocic properties. Patented in 1950.

Case report

- Hill and Malkasian (1979): 1 healthy newborn exposed throughout pregnancy.

Retrospective cohort studies with internal controls

- Rosa (1993), Michigan, MSS: of 17 first trimester exposures, 1 newborn with major defects, 1 expected (RR = 1.0; CI 95%: 0.0-5.6).

Feto-neonatal effects: we have located case reports in literature concerning exposures in the second half of pregnancy (Spinnato et al 1984, Wong et al 1992, Wang et al 1995). One exposed newborn showing trombocytopenia (Domula et al 1977) and one case of maternal fulminant hepatitis (Bourlière et al 1988) have been reported.

Disopyramide – C01BA03

Patented in 1961.

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

Case report

- Shaxted and Milton (1979): 1 exposure during the early 14 weeks of pregnancy with no adverse outcomes in the newborn.

Studies on laboratory animals

- Umemura et al (1981): nonteratogenic in rats (30 mg/kg).
- Esaki et al (1981): nonteratogenic in rabbits (11 mg/kg).

Feto-neonatal effects: this drug may cause an increase in uterine contractions late in pregnancy, as well as rupture of the placenta and premature birth (Leonard et al 1978, Tadmor et al 1990 and Abbi et al 1999).

Dihydroquinidine – C01BA49

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.

Mexiletine – C01BB02
Patented in 1967.

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

Case report

- Lownes and Ives (1987): 1 newborn exposed throughout pregnancy.
- Lewis et al (1981): 1 healthy newborn exposed since week 14.

Feto-neonatal effects: 1 newborn exposed since week 32 with no adverse outcomes (Timmis et al 1980)

Propafenone – C01BC03

Patented in 1970.

Cohort studies without controls

- Knoll (1993), manufacturer: of 37 exposures (period of intake not specified), 24 healthy newborns, 3 newborns with neonatal impairments, 3 newborns with congenital anomalies (labio-cleft palate exposed in the second trimester. Hydrocephaly, microcephaly with large hands and feet, also exposed to levothyroxine).

Feto-neonatal effects: 1 exposure in the second and third trimester had no adverse outcomes (Brunozzi et al 1988).

Flecainide – C01BC04

Patented in 1974.

Case report

- Wagner et al (1990): 1 exposure throughout pregnancy.
- Villanova et al (1998): 1 exposure throughout pregnancy.
- Poral et al (2003): 1 exposure in week 13 and 14.

Cohort studies without controls

- 3M Pharmaceuticals (1990), manufacturer: of 20 newborns exposed throughout pregnancy, 19 were healthy, 1 had transitory DIV. Of 15 first trimester exposures, 5 spontaneous abortions, 9 healthy newborns, 1 newborn with not specified cardiac defect. Of 27 second and third trimester exposures, 23 healthy newborns, 2 intrauterine deaths, 1 talipes varus and 1 newborn with neurological deficiency.

Feto-neonatal effects: there are many reports concerning newborns exposed after week 21 with no adverse outcomes either in the mother or in the fetus (Wren and Hunter 1988, Allan et al 1990, Kofinas et al 1991, Smoleniec et al 1991, Perry et al 1991, Mills 1992, Connaughton and Jenkins 1994, van Engelen et al 1994, Kohl et al 1995, Baroffio et al 1996, Ahmed et al 1996, Amano et al 1997, Hamel et al 1997, Won et al 1998, Simpson and Sharland 1998, Edwards et al 1999, Fesslova et al 2000, Midgley and Harding 2000, Vautier-Rit et al 2000, Ebenroth et al 2001, D'Souza et al 2002, Krapp et al 2002, Oudijk et al 2003). Elevated hyperbilirubinemia in one exposure late in pregnancy (Vanderhal et al 1995), alterations of the cardiac rhythm (Van Gelder-Hasker et al 1995), intrauterine fetal death (Allan et al 1990).

Amiodarone – C01BD01

This is a liposoluble slow-elimination substance. The therapeutic dose (400 mg/die) determines the intake of 12 mg of iodine. Iodine interferes with the biosynthesis of thyroid hormones, thus after the 10th week of pregnancy it may cause transitory hypothyroidism and congenital goiter. Due to its long life in the body, this substance may influence the growth of the thyroid also in case of intake prior to week 10. It is used in the treatment of maternal and fetal arrhythmia. Patented in 1962.

Case report

- Haffaiee (1983), Laurent et al (1987, de Wolf et al (1988): 3 newborns showing congenital hypothyroidism, exposed at different stages of pregnancy.
- 16 newborns have been reported with no thyroid problems, exposed to amiodarone in the first trimester (Rey et al 1985, Robson et al 1985, Penn et al 1985, Strunge et al 1988, Widerhorn et al 1991, Valensise et al 1992) and later in pregnancy (Candelpergher et al 1982, McKenna 1983, Pitcher et al 1983, Robson 1985, Wladimiroff and Steward 1985, Arnoux et al 1987, Rey et al 1987, Foster and Love 1988, Gembruch et al 1989, Flack et al, 1993, Fulgencio and Hamza 1994, Tomek et al 2002).
- Ovadia et al (1994): of 2 exposures throughout pregnancy, 1 healthy newborn and 1 with severe cardiovascular defect.
- Plomp et al (1992): 4 healthy newborns exposed throughout pregnancy and 1 newborn with hypothyroidism exposed since week 34.

Retrospective cohort studies without controls

- Matsumura et al (1992): of 9 healthy newborns, one revealed T3 and TSH altered values, but with clinical symptoms of hypothyroidism that got back to normal within one month of age. None of the 9 studied babies had T3 and TSH altered values at 3, 6, 9 and 12 months of age.
- Magee et al (1995): of 11 exposed newborns, 6 had been also exposed to beta-blockers. 1 newborn had hypothyroidism and 1 had hyperthyroidism; 4 appeared small as per their gestational age. Besides, 1 newborn who had also been exposed to propranolol and quinidine in the first trimester had a congenital anomaly (nystagmus and head tremor) whereas 1 newborn who had also been exposed to atenolol and phenoxibenzamine since the 20th week had hypotonia, hypertelorism and micrognathia.

Feto-neonatal effects: bradycardia in second and third trimester exposures (Rey et al 1985, Robson et al 1985).

Conclusions: Available data in literature and chemical characteristics of this substance show a possible association between the use of amiodarone in pregnancy and hypothyroidism / congenital goiter or hyperthyroidism. These alterations are to be attributed to iodine contained in the substance. Iodides can alter fetal thyroid function when administered after week 10 of pregnancy (12th-14th week), that is when iodine starts to be collected by the fetal thyroid (Hobel 1980). The drug long half-life (15-58 days) can affect the thyroid growth also in case it has been taken earlier. Thyroid dysfunction can be assumed in the second trimester of pregnancy if there is a delay in the bone growth (De Wolf et al 1988). Thyroid function should be controlled in newborns exposed to amiodarone.

C01B class conclusions: There is no written evidence of any association between anti-arrhythmic drugs (except for amiodarone, which deserves a separate evaluation) and population background reproductive risk. In case of exposure an increase in the risk is not even likely, due to the available studies concerning some substances in this group. Besides, a lack of reported anomalies over the long period of commercialization should be considered, and the absence of teratogenic effects in laboratory animals (records provided by manufacturer for registration, not available in databases).

C01C – Cardiac stimulants, excluding cardiac glycosides

C01CA – Adrenergic and dopaminergic agents

High dosages of sympathomimetic amines having alpha-effect, also when locally used, can cause systemic effects such as uterine vessels constriction and consequent uterine hypo-perfusion. Beta-2-receptors sympathomimetics are believed to inhibit uterine muscles.

Ethylefrine – C01CA01

Patented in 1929

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.

Oxedrine – C01CA08

Patented in 1929.

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.

Ibopamine – C01CA16

Patented in 1976.

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

Midodrine – C01CA17

Patented in 1964.

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.

Adrenaline (Epinephrine) – C01CA24

This agent is normally contained in the body. Patented in 1903.

Case report

- Hernandez et al (1980): 1 premature healthy newborn exposed from week 1 to 13th to cromoglycate and adrenaline.

Retrospective cohort studies with internal controls

- Rosa (1994), Michigan MSS: of 35 first trimester exposures, none was born with major defects, 1.5 expected (RR = 0.0; CI 95%: 0.0-2.5).

Prospective cohort studies with internal controls

- Heinonen et al (1977), CPP: of 189 exposures in the early 16 weeks, 14 newborns had congenital defects (ARR = 1.6; CI 95%: 1.0-2.7).

Feto-neonatal effects: Adrenaline can be responsible for uteroplacental vasoconstriction and consequent fetal hypoxia and tetanic spasm of uterine muscles. One newborn exposed at week 28 is reported to have a lessening in fetal movements and intracranial hemorrhage. He died on day 4 (Entman and Moise 1984).

Conclusions: This drug is not considered teratogenic in human by many authors (Nishimura and Tanimura 1976, Shepard 1983, Perry and Kaambam 1990). ADEC, FASS and WGZ consider it a drug of choice in pregnancy.

C01B class conclusions: There is no written evidence of any association between drugs in this therapeutic group and population background reproductive risk. In case of exposure an increase in the risk is not even likely, due to the available studies concerning some substances in this group. Besides, a lack of reported anomalies over the long period of commercialization should be considered, and the absence of teratogenic effects in laboratory animals (records provided by manufacturer for registration, not available in databases).

C01D – Vasodilators used in cardiac diseases

C01DA – Organic nitrates

Nitroglycerin – C01DA02

This organic nitrate is also used as short-action tocolytic at birth. Available in Italy since 1984.

Prospective cohort studies with internal controls

- Heinonen et al (1977), CPP: this agent has been studied along with 15 more vasodilators in a total of 15 exposures 7 of which to nitroglycerin during the early 16 weeks. 2 newborns had congenital anomalies (ARR for the entire group of vasodilators = 2.6; CI 95%: 0.7-9.6).

Feto-neonatal effects: This drug has been used after the first trimester to treat infarct, pregnancy hypertension and preeclampsia (Cotton et al 1986a, Longmire et al 1991, Ottman and Gall 1993, Sheikh and Harper 1993, Sanchez-Ramos et al 1994, Grunewald et al 1995, Facchinetti et al 1996) and the results have been good. In some cases fetal deceleration and bradycardia has occurred (Cotton et al 1986b).

Penta-erythrityl tetranitrate – C01DA05

This is an organic nitrate. Patented in 1943.

Prospective cohort studies with internal controls

- Heinonen et al (1977), CPP: this substance has been studied along with other vasodilators in a total of 15 exposures 3 of which to penta-erythrityl during the early 16 weeks. 3 newborns had congenital anomalies (ARR for the entire group of vasodilators = 2.6; CI 95%: 0.7-9.6).

Isosorbide dinitrate – C01DA08

Isosorbide mononitrate – C01DA14

This is an organic nitrate. Patented in 1939.

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.

Tenitramine – C01DA38

This is an organic nitrate. 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.

Heptaminol – C01DX08

Patented in 1947.

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.

Trapidil – C01DX11

Available in Italy since 1990.

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

C01D class conclusions: There is no written evidence of association between drugs in this therapeutic group and population background reproductive risk. In case of exposure an increase in the risk is not even likely, due to the available studies concerning some substances in this group. Besides, a lack of reported anomalies over the long period of commercialization should be considered, as well as the absence of teratogenic effects in laboratory animals (records provided by manufacturer for registration, not available in databases).

C01EB – More cardiac preparations

Phosphocreatine – C01EB06

Available in Italy since 1987.

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

Fructose 1,6-diphosphate – C01EB07

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.

Ubidecarenone – C01EB09

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.

Adenosine – C01EB10

This is a purine nucleoside and it is found in RNA.

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: it is used to treat maternal or fetal supraventricular tachycardia at any stage of pregnancy with no adverse effects on either the mother or the fetus (Briggs et al 2002).

Trimetazidine – C01EB15

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.

C01EB class conclusions: There is no written evidence of any association between drugs in this therapeutic group and population background reproductive risk. In case of exposure an increase in the risk is not even likely, due to the available studies concerning some substances in this group. Besides, a lack of reported anomalies over the long period of commercialization should be considered, and the absence of teratogenic effects in laboratory animals (records provided by manufacturer for registration, not available in databases).

C02 – Antihypertensive drugs

C02A – Centrally acting adrenergic drugs

Methyldopa – C02AB01 – C02AB02

Patented in 1953.

Case report

- Ylikorkala (1975): 1 newborn with multiple defects (esophageal atresia, tracheal fistula, cardiopathy, hypospadias, left kidney agenesis) also exposed to clomiphene in the first trimester of pregnancy.
- Rosa et al (1987): 1 newborn exposed to minoxidil, methyldopa, hydralazine, furosemide and phenobarbital, showing transposition of the great vessels and pulmonary stenosis.

Cohort studies without controls

- Gallery et al (1985): 87 exposures to methyldopa (8 since the first trimester), 96 to oxprenolol (9 since the first trimester), 4 neonatal deaths among exposed to methyldopa.

Retrospective cohort studies with internal controls

- Rosa et al (1993), Michigan MSS: of 242 first trimester exposures, 11 newborns with major defects, 10 expected (RR = 1.1; CI 95%: 0.5-2.0).

Prospective cohort studies with internal controls

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

Feto-neonatal effects: reduced skull girth in exposures after the first trimester (Moar et al 1978, Myerscough 1980) and a reduction of 4-5 mg/Hg in pressure (Whitelaw 1981), stillbirth (Gallery et al 1979), no unwilling outcomes in 75 exposed newborns (Torley et al 1981, Williams et al 1983). 1 newborn has been reported with multiple malformations (oligohydramnios, reduced intrauterine growth, post-natal anuresis, hypocalvaria and articular contracture), who had been exposed after the first trimester also to captopril and furosemide (Rothberg and Lorenz 1984). 1,157 exposures at different stages of pregnancy resulted with no adverse effects on the fetus (Briggs et al 2001).

Conclusions: Available studies on first trimester exposure do not uncover any increase in the population background reproductive risk.

C02AC – Antagonists of imidazoline receptors

Clonidine – C02AC01

Patented in 1961

Case report

- Stoll (1979): 1 first trimester exposure with multiple malformations.

Retrospective cohort studies with internal controls

- Huisjes et al (1986): 22 children aged from 4 years and 9 months and 7 years and 9 months exposed during pregnancy were compared with 22 non-exposed controls. No differences were recorded as per skull girth, neurological problems, school attitudes and behavioral problems (except for hyperactivity and sleep disorders in the studied group).

- Rosa (1993), Michigan MSS: of 59 exposures in the first trimester, 3 newborns had major defects while 3 are expected (RR = 1.1; CI 95%: 0.5-2.0).

Feto-neonatal effects: 84 exposures between 23rd week and birth have been reported showing no adverse outcomes in either the mother or the newborn (Turnbull and Ahmed 1970, Johnston and Aickin 1971, Pietropaolo et al 1972, Leighton and Tighe 1974, Harvath et al 1985, Hartikainen- Sorri et al 1987). Behavioral disorders such as hyperactivity and insomnia were reported in babies exposed at the end of pregnancy (Huisjes 1986). Transitory 3-days long hypertension was reported in a baby exposed at the end of pregnancy (Boutry et al 1988).

Conclusions: Available studies on first trimester exposure to clonidine do not uncover any increase in the population background reproductive risk.

C02C – Adrenergic drugs with peripheral action

C02CA – Alpha-adrenergic receptor blockers

Doxazosin – C02AC04

It is available in Italy since 1989.

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

Studies on laboratory animals

- Horimoto and Ohtsuki (1990): this agent appears to be nonteratogenic in either rats (up to 120 mg/kg per os) or rabbits (up to 100 mg/kg per os).

Terazosin – C02CA49 – G04CA03

It is available in Italy since 1989.

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

Studies on laboratory animals

- Solvetti (1990): this agent has shown to be nonteratogenic in rabbits (165-1,330 times the therapeutic human dose per os). Fetal re-absorption occurred in rats exposed to 480 mg/kg/die (1,330 times the therapeutic human dose per os).

C02CA class conclusions: There is no written evidence of any association between drugs in this therapeutic group and population background reproductive risk. In case of exposure an increase in the risk is not even likely, due to the available studies concerning some substances in this group. Besides, a lack of reported anomalies over the long period of commercialization should be considered, and the absence of teratogenic effects in laboratory animals (records provided by manufacturer for registration, not available in databases).

C02D – Drugs acting on arteriolar smooth musculature

Cadralazine – C02DB04

It is available in Italy since 1987.

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

Conclusions: There is no written evidence of specific studies concerning the use of cadralazine in human pregnancy. In case of exposure an increase in the risk is not even likely, due to the available studies concerning some substances in this group. Besides, a lack of reported anomalies over the long period of commercialization should be considered, and the absence of teratogenic effects in laboratory animals (records provided by manufacturer for registration, not available in databases).

Minoxidil – C02DC01 –D11AX01

This is a pyrimidine derivative. Patented in 1965.

Case report

- Valdivieso et al (1985): 1 healthy newborn exposed throughout pregnancy.
- Kale et al (1987): 1 newborn exposed throughout pregnancy to minoxidil, captopril and propranolol due to maternal hypertension presented hypertrichosis, onphalocele, DIV, facial dimorphism (nasal hypoplasia and micrognathia), retained testis, 5th finger clinodactyly. Hypertrichosis was transitory in the follow-up.
- Rosa et al (1987): 1 newborn of 32 weeks who had been exposed throughout pregnancy to minoxidil, methyl dopa, hydralazine, furosemide and phenobarbital died of transposition of the great vessels and pulmonary stenosis. 1 healthy newborn showing hypertrichosis (reduced in two-month time) had been exposed throughout pregnancy to minoxidil, metoprolol and prazosin.
- Veyrac et al (1995): 1 newborn exposed to topic minoxidil during most of pregnancy had hypertrichosis.
- Rojansky et al (2002): 1 fetus with caudal regression syndrome (aplasia of the sacral tract of the backbone and renal agenesis) had been exposed throughout pregnancy to a minoxidil-based hair lotion and in the first trimester to trimethoprim + sulphamethoxazole.
- Smorlesi et al (2003): 1 fetus showing diffuse cerebral anomalies (intracerebral hemorrhage, multiple necrosis and demyelination areas), cardiac hypertrophies with subaortic stenosis, common mesentery and extended sigmoid colon had been exposed throughout pregnancy, every other day, to a 2% minoxidil-based hair lotion.

Conclusions: There are few reports in literature concerning newborns showing single hypertrichosis and/or other congenital anomalies. Hypertrichosis is attributable to this drug, being a side effect of minoxidil, used locally to treat Hippocratic baldness (Price 1999). As a topical agent it has a systemic pharmacological outcome (Leenen et al 1988) and can cross the placenta at such a toxicological concentration as to affect the fetus. It is impossible to tell that topical minoxidil was a causative agent also of other malformations. The only common malformation to all 7 cases was a congenital cardiopathy.

C02K – More antihypertensive drugs

Dihydroergotoxine – C02KA49 – C04AE01

This is a mixture of natural alkaloids semisynthetic derivatives: dihydroergocornine, dihydroergocristine and dihydroergocriptine. Dihydroergotoxine alkaloids do not have a uterotonic activity, like natural alkaloids, they rather have a tocolytic activity, probably being stimulated by uterine beta-receptors. Patented in 1940.

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.

Ketanserin – C02KD01

This is a serotonin antagonist, available in Italy since 1987.

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

C02K class conclusions: There is no written evidence of any specific study concerning the use of drugs in this therapeutic group in human pregnancy. 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).

Reserpine – C02LA01

Patented in 1953.

Case report

- Pauli and Petersen (1986): 1 newborn exposed during the first 6 months of pregnancy was showing craniofacial, abdominal and CNS abnormalities.

Cohort studies without controls

- Sobel (1960): of 15 exposures (non-specified period), all healthy newborns but one stillbirth and 2 twins with congenital lung cysts.

Retrospective cohort studies with internal controls

- Rosa (1993), Michigan MSS: of 15 first trimester exposed newborns, none of them had congenital anomalies, 1 is expected (RR = 0.0; CI 95%: 0.0-3.7).

Prospective cohort studies with internal controls

- Heinonen et al (1977), CPP: of 48 exposures in the first 16 weeks, 4 were babies with congenital anomalies (ARR = 1.7; CI 95%: 0.7-4.4).
- Czeizel (1988), Hungarian CCSCA: 60 exposed pregnancies have been studied (the period of exposure not being specified). There was no increase in congenital anomalies in comparison with the control group of 9,892 newborns.

Feto-neonatal effects: reserpine administration late in pregnancy can cause nasal stuffiness, lethargy, hypotension, bradycardia and neonatal respiratory failure (Budnick et al 1955).

Conclusions: There is no written evidence of association between reserpine and increase in the population background reproductive risk. In case of exposure the 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).

C03 – Diuretics

These drugs increase urinary flow rate in the following: proximal tubule (carbonic anhydrase-inhibitor and osmotics), Henle's ansa (osmotics), ascending tract of the ansa (symporter Na⁺ - K⁺ - 2Cl-inhibitors), distal convoluted tubule (thiazides and thiazides-like), distal final tubule and collecting duct (potassium saver and aldosterone antagonists).

Case-control studies, nonspecific

- Nelson and Forfar (1971): 458 newborns with congenital anomalies (175 major and 283 mild) have been matched with 911 healthy controls. 2 newborns exposed to diuretics in the first trimester had congenital anomalies (1 of which was a major defect) vs. 2 healthy exposed controls (OR = 2.0; CI 95%: 0.1-27.6).

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

- Kallen and Otterblad Olausson (2003), Swedish MBR: 5,015 newborns with cardiovascular abnormalities were matched with 577,730 newborns in total (OR for exposure to diuretics in the first trimester = 2.3; CI 95%: 1.6-11.7).

C03A – Low acting diuretics, thiazides

C03AA – Thiazides, not associated

Hydrochlorothiazide C03AA03 –C03EA01

It is available in Italy since 1958.

Case report

- Robson et al (1985): 1 healthy newborn exposed throughout pregnancy to amiloride, hydrochlorothiazide and amiodarone.

Retrospective cohort studies with internal controls

- Rosa (1993), Michigan MSS: of 567 first trimester exposures, 24 newborns had major defects and 22 are expected (RR = 1.1; CI 95%: 0.7-1.6).

Prospective cohort studies with internal controls

- Heinonen et al (1977), CPP: of 107 exposures in the early 16 weeks, 7 newborns had congenital anomalies (ARR = 1.4; CI 95%: 0.7-2.8).

Feto-neonatal effects: In the late period of pregnancy thiazides can induce neonatal hypoglycemia subordinated to maternal hyperglycemia (Senior et al 1976) as well as trombocytopenia (Menzies 1964, Harley et al 1964, Rodriguez et al 1964, Leikin 1964, Prescott 1964, Cuadros and Tatum 1964, Jones and Reed 1965, Finnerty and Bepko 1966, Kraus et al 1966, Gray 1968, Karpatkin et al 1972), electrolytic impairments (hypo-Natriemia and hypo-Kaliemia) (Pritchard and Walley 1961, Alstatt 1965, Anderson and Hanson 1974), hemolytic anemia (Harley et al 1964), acute pancreatitis (Minkowitz et al 1964).

Conclusions: There is no written evidence of association between intake of hydrochlorothiazide in pregnancy and increase of population background reproductive risk. Also in consideration of 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), such an association is not likely. When administered late in pregnancy thiazides can induce neonatal hypoglycemia subordinated to

maternal hyperglycemia, as well as thrombocytopenia, electrolytic impairments, hemolytic anemia and acute pancreatitis.

C03B – Low acting diuretics, apart from thiazides

C03BA – Sulphonamides, not associated

Chlorothalidone – C03BA04

Patented in 1962.

Cohort retrospective studies with internal controls

- Rosa (1993), Michigan MSS: of 48 exposures in the first trimester, 2 were born with major defects and 2 are expected (RR = 1.0; CI 95%: 0.1-3.6).

Metolazone – C03BA08

Patented in 1966.

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

Studies on laboratory animals

- Nakajima et al (1978 a, b): dilatation of urinary pelvis in rats (2 mg/kg/die: 25 times the human therapeutic dose); nonteratogenic in rabbits (10 mg/kg).

Xipamide – C03BA10

It is available in Italy since 1985.

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

Indapamide – C03BA11

Patented in 1971.

Retrospective cohort studies with internal controls

- Rosa (1993), Michigan MSS: of 46 first trimester exposures, 3 newborns had major defects, 2 are expected (RR = 1.5; CI 95%: 0.3-4.4)

Fenquizone – C03BA13

Patented in 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.

C03BA class conclusions: As for some agents in this therapeutic group there are no available specific studies concerning their use in human pregnancy; other agents have been more or less studied, instead. 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), an increase in the population background reproductive risk is not likely.

C03C – High acting diuretics

C03CA – Sulphonamides, not associated

Furosemide – C03CA01 – C03B01

Patented in 1962.

Retrospective cohort studies with internal controls

- Rosa (1993), Michigan MSS: of 350 first trimester exposures, 18 had major defects and 15 are expected (RR = 1.2; CI 95%: 0.7-1.9).

Feto-neonatal effects: this drug has been used after the first trimester for edema, hypertension and toxemia of pregnancy with no adverse effects on fetus or newborn (Briggs et al 2002).

Piretadine – C03CA03

Patented in 1977.

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.

Torasemide – C03CA04

It is available in Italy since 1993.

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

Studies on laboratory animals

- Ohta et al (1994): costal anomalies in rats (30 mg/kg/die).

C03CC – Aryl-oxoacid derivatives

Ethacrynic acid – C03CC01

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.

Case report

- Jones (1973): a single case has been reported of maternal and neonatal ototoxicity in a woman treated at the 28th week of pregnancy with ethacrynic acid and 4-5 g in total of kanamycin.

C03CX – More high acting diuretics

Etozolin – C03CX01

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.

C03CA – CC- CX class conclusions: There is no written evidence of specific studies concerning the use of drugs in this therapeutic group during pregnancy. In case of exposure the population background risk increase 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).

C03D – Potassium sparing drugs

C03DA – Aldosterone antagonists

Spirolactone – C03DA01 – C03EB01

This agent has antiandrogen effects in humans. Patented in 1961.

Studies on laboratory animals

- Messina et al (1979): feminization syndrome in male fetuses of rats.

Retrospective cohort studies with internal controls

- Rosa (1993), Michigan MSS: of 31 first trimester exposures, 2 were born with major defects, 9 are expected (RR = 0.2; CI 95%: 0.0-0.8).

Potassium canrenoate – C03DA02 – C03EA14

It is available in Italy since 1978.

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.

Canrenone – C03DA03

It is available in Italy since 1983.

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.

Amiloride – C03DB01

This agent is a sodium inhibitor in renal epithelium. Patented in 1967.

Case report

- Duminy and Burger (1981): a single fetus exposed in the first trimester to propanol, amiloride and captopril was showing limb and skull (VIP) defects.
- Almeida and Spinnato (1989), Robson et al (1985): 2 healthy newborns exposed throughout pregnancy

Retrospective cohort studies with internal controls

- Rosa (1993), Michigan MSS: of 28 first trimester exposures, 2 newborns had major defects and 1 is expected (RR = 2.0; CI 95%: 0.7-7.2).

Triamterene – C03DB02 – C03EB01

This agent is a sodium inhibitor in renal epithelium. It is also a mild antagonist of folic acid. Patented in 1963.

Prospective cohort studies with internal controls

- Heinonen et al (1977), CPP: 5 healthy newborns exposed during the first 16 weeks of pregnancy.

Retrospective cohort studies with internal controls

- Rosa (1993), Michigan MSS: of 318 exposed in the first trimester, 15 had major defects, 13 are expected (RR = 1.1; CI 95%: 0.6-1.9).

C03E – Diuretics and Potassium sparing drugs in association

Butizide – C03EA14 – C02LB01

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.

C03D – C03E class conclusions: As for some agents in this therapeutic group there are no available specific studies concerning their use in human pregnancy; other agents have been more or less studied, instead. 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), an increase in the population background reproductive risk is not likely.

C04A – Peripheral vasodilators

C04AD – Purine derivatives

Nicotine xanthinol – C04A202

Patented in 1960.

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

Studies on Laboratory animals

- Taniguchi et al (1974): nonteratogenic in rats (10,000 mg/kg per os; 1240 mg/kg administered subcutis) or in mice (5,000 mg/kg per os 1,250 mg/kg administered subcutis).

Pentoxifylline – C04AD03

This synthetic xanthine increases sperm motility (Shen et al 1991). Patented in 1969.

Retrospective cohort studies with internal controls

- Rosa (1993), Michigan MSS: of 34 first trimester exposures, 5 newborns had major defects, 1 is expected (RR = 5.01; CI 95%: 1.6-11.7).

C04AE – Ergot alkaloids

Nicergoline – C04AE02

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.

Dihydroergocristine – C04AE04

Patented in 1943.

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.

C04AX – More peripheral vasodilators

Cyclandelate – C04AX01

Patented in 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.

Vincamine – C04AX07

Patented in 1972.

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.

Piribedil – C04AX13

Patented in 1967.

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

Vinburnine – C04AX17

It is available in Italy since 1985.

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

Buflomedil – C04AX20

Patented in 1971.

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

Studies on laboratory animals

- Fukushima et al (1994 a, b): nonteratogenic in rats (250 mg/kg/die) or in rabbits (100 mg/kg per os).

Naftidrofuril – C04AX21

It is available in Italy since 1984.

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

Studies on laboratory animals

- Fontaine et al (1979): nonteratogenic in mice (360 mg/kg) or in rats (480 mg/kg) and in rabbits (5 mg/kg).
- Umemura et al (1985 and 1986): nonteratogenic in rats (600 mg/kg intramuscular administered) or rabbits (2-mg/kg intramuscular administered and 400 mg/kg per os).

Raubasine – C04AX49

It is available in Italy since 1981.

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

C04A class conclusions: There is no written evidence of specific studies concerning the use of peripheral vasodilators in human pregnancy. In case of exposure the population background risk increase 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).

C05 – Vasoprotectors

C05C – Capillary-protectors

C05CA – Bioflavonoids

Bioflavonoids are ubiquitous pigments traceable in many vegetable species. There are over 4,000 of them in nature. Among the most common ones, found in some drugs, rutin, diosmin and hesperidin are to be mentioned. They are used to treat varicose veins and hemorrhoids.

Laboratory experimental studies

- Strick et al. (2000): some flavonoids are believed to induce chromosomal abnormality in hemopoietic undifferentiated cells and specific cell lines inhibiting topoisomerase II on MLL gene. Chromosomal abnormality (band 11q23) related to MLL gene, are in fact mostly present in infant leukemia. Such an imaginative hypothesis is well analyzed in BIF by Anonymous (2002) and Clementi (20003).

Diosmin – C05CA03

It is available in Italy since 1987.

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

Feto-neonatal effects: Exposures after the first trimester have been studied and no adverse outcomes have been noticed in human pregnancy, as far as fetal growth, neonatal weight and neonatal growth (Bucksee et al 1997).

Troxeutin – C05CA04

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.

Mirtillina POTREBBE ESSERE “BILBERRY”? (Myrtocyan) – C05CA49

It is available in Italy since 1984.

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

Oxerutin – C05CA49

It is available in Italy since 1972.

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.

Rutoside – C05CA51

It is available in Italy since 1971.

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.

Aminaftone – C05CX

It is 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.

Calcium dobesilate – C05CX

It is available in Italy since 1973.

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.

Centasine – C05CX

It is available in Italy since 1984.

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

Chromium carbonyl / Chromic carbonate/ ?? – C05CX

It is 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.

Escina – C05CX

Patented in 1955.

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.

C05C class conclusions: There is no written evidence of specific studies concerning the use of capillary-protectors in human pregnancy. In case of exposure the population background risk increase 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).

C07 – Beta-blockers

Beta-blockers are inhibitors of cardiac beta-receptors acting to obtain an isotropic and chronotropic negative effect. They work to reduce pressor response mediated by the sympathetic system and consequently to regulate the control of peripheral baroreceptors.

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

- Kallen and Otterblad Olausson (2003), Swedish MBR: 5,015 cases of newborns with cardiovascular defects, 25 of whom exposed in the first trimester to beta-blockers were studied along with 577.730 controls, 1,548 of whom had been exposed. OR = 1.9 (CI 95%: 1,2-2.8), was interpreted as due to the confounding outcome of maternal hypertension or to multiple matching.

Feto-neonatal effects: metanalysis of two trials (100 exposures, 104 controls) (Butters et al 1990, Sibai et al 1990) (RR for small As per gestational age exposed to beta-blockers = 2.5; IC 95%: 1.6-6.0) (Magee 2001).

C07AA – Non selective beta-blockers.

Pindolol – C07AA03

Patented in 1965.

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

Studies on laboratory animals

- Shardein et al (2000): the agent proved to be non-fetotoxic, nor teratogenic in rabbits, mice, or rats.

Feto-neonatal effects: There has not been a reduction in fetal heart rate (Ingemarsson et al 1984); neonatal bradycardia was noticed (Monton et al 1992), as well as moderate change in fetal hemodynamic function after maternal intake e.v. (Rasanen and Jouppila 1995); average neonatal weight was higher vs. exposures to acebutol and atenolol (Bubois et al 1982).

Propranolol – C07AA05

Patented in 1963.

Case report

- Buminy and Burger (1981): 1 fetus exposed in the first trimester to propranolol, captopril and amiloride had limb and skull congenital defects.
- Bott-Kanner et al (1978): 1 newborn exposed throughout pregnancy had hypertrophic stenosis of pylorus.
- O'Connor et al (1981): 1 newborn exposed throughout pregnancy showing dysplasia of the hip.
- Campbell (1985): 1 newborn exposed throughout pregnancy had tracheoesophageal fistula.

Retrospective cohort studies with internal controls

- Rosa (1993), Michigan MSS: of 274 newborns exposed in the first trimester there were 11 newborns with congenital anomalies and 12 are expected (RR = 0.0; CI 95%: 0.5-1.6).

Feto-neonatal effects: the survey of 23 studies/reports on a total of 167 newborns chronically exposed has uncovered the following malformations. IUGR (14%), respiratory distress (4%), bradycardia (7%), hypoglycemia (10%), hyperbilirubinemia (4%) and polycythemia (1%), thrombocytopenia (1%) (Cottrill et al 1977, Eliahou et al 1978, Pruyn et al 1979, Paran et al 1995). Reduced neonatal weight was noticed in exposures throughout pregnancy (Paran et al 1995, Pruyn et al 1979), as well as prematurity (Tunstall 1969, Goodlin 1982) and fetal bradycardia (Mitrani et al 1975).

Timolol – C07AA06

Patented in 1969.

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

Studies on laboratory animals

- USP DI (2001): nonteratogenic in mice, rats or rabbits.

Feto-neonatal effects: bradycardia and fetal arrhythmia (intraocular exposure) (Wagenvoort et al 1998), hypocalcemia, hypomagnesemia and metabolic acidosis (intraocular exposure and exposed to acetazolam per os) (Merlob et al 1990), metabolic acidosis (Devoe et al 1986).

Sotalol – C07AA07

Patented in 1966.

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

Case report

- Babin et al (1985): 1 newborn exposed throughout pregnancy showing facial dysmorphism, microcephaly, tracheal stenosis, and cardiac arrhythmia.
- Wagner et al (1990): 1 healthy newborn exposed throughout pregnancy.

Studies on laboratory animals

- Ifarashi et al (1955), Kawanishi et al (1955): nonteratogenic in rats or rabbits.

Feto-neonatal effects: this agent has been successfully employed in the treatment of fetal tachyarrhythmia in the second and third trimester (Meijboom et al 1994, Jaeggi et al 1998, Sonesson et al 1998, Oudijk et al 2000); neonatal bradycardia (O'Hare et al 1980).

Nadolol – C07AA12

Patented in 1971.

Prospective cohort studies with internal controls

- Rosa (1993), Michigan MSS: of 71 newborns exposed in the first trimester, 1 had congenital anomalies, 3 are expected (RR = 0.3; CI 95%: 0.0-1.9).

Feto-neonatal effects: IUGR, cardiorespiratory depression, tachypnea, hypothermia and hypoglycemia were noticed in an exposure throughout pregnancy to nadolol, triamterene, hydrochlorothiazide and thyroid hormones (Fox et al 1985).

Indenolol – C07AA49

It is available in Italy since 1986.

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.

C07AB – Selective beta-blockers

Metoprolol – C07AB02-C07BB02-C07CB02

It is available in Italy since 1978.

Case report

- Czeizel et al (1997): 1 newborn exposed at the 4th week to overdose of the drug had bilateral cryptorchidism.

Feto-neonatal effects: low neonatal weight (Suonio 1986, Sandstrom 1982, Czeizel and Toth 1998). 1 newborn exposed at the 20th week to overdose, and chronic abuse of this drug and of alcohol had microcephaly and convulsions (Czeizel et al 1977). 160 healthy newborns showing no problems at all exposed after the first trimester (Jannet et al 1994, Wichman et al 1984, Hogstedt et al 1985, Oumachigui et al 1992).

Atenolol – C07AB03-C07CB03-C07FB03

Patented in 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.

Case report

- Satge et al (1997): 1 newborn exposed since the second month of pregnancy had retroperitoneal fibromatosis.
- Briggs and Nageotte (2001): 1 missed labor at the 33rd week, exposed throughout pregnancy to valsartan and atenolol, showing anhydramnios, hypoplasia of the placenta and pulmonary hypoplasia (attributable to valsartan).

Feto-neonatal effects: IURG (Dubois et al 1983, Butters et al 1990), intrauterine growth delay and fetal bradycardia, and low neonatal weight (Rubin et al 1983, Ingemarsson et al 1984, Montan et al 1992, Lip et al 1997, Lydakis et al 1999, Magee 2001). Low neonatal weight in exposures in the first trimester, but not in the exposures of the second trimester (Easterling et al 2001, Bayliss et al 2002). Moderate change in fetal hemodynamic function following intravenous administration due to maternal hypertensive crisis (Rasanen and Jouppila 1995).

Acebutolol – C07AB04

Patented in 1968.

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

Case report

- Boutroy et al (1984): 1 newborn exposed throughout pregnancy to captopril and acebutolol, showing patent ductus arteriosus, fetal reduced growth, respiratory arrest at birth and several hypotensive episodes.

Studies on laboratory animals

- Yokoi et al (1978): nonteratogenic in rats (25 mg/kg/die e.v.; 500 mg/kg/die per os).

Feto-neonatal effects: the following malformations have been reported in exposures after the first trimester: hypotension. Bradycardia and renal function impairment, during the first days of life (Dumez et al 1981, Yassen et al 1992); neonatal hypoglycemia (Williams et al 1983); lower neonatal weight in comparison with those exposed to pindolol, but higher compared to those exposed to atenolol (Dubois et al 1982).

Betaxolol – C07AB05

It is available in Italy since 1985.

Retrospective cohort studies without controls

- Boutroy et al (1990): 23 healthy newborns exposed to this agent throughout pregnancy.

Bisoprolol – C07AB07

It is available in Italy since 1989.

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

Studies on laboratory animals

- Suzuki et al (1989): nonteratogenic in rats or rabbits.

Celiprolol – C07AB08

Available in Italy since 1998.

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

Studies on laboratory animals

- Ninomiya et al (1989 a, b, c): nonteratogenic in rats.

Nebivolol – C07AB12

It is 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.

C07AG – Adrenergic alpha- and beta-blockers

Labetalol – C07AG01 – C07CG01

Patented in 1970.

Case report

- Crooks et al (1998): 2 newborns exposed throughout pregnancy had pericardial effusion, myocardial hypertrophy and clinical symptoms of beta-block. 1 of the two died, the other recovered in 6 weeks.

Retrospective case-controls with internal controls

- Rosa (1993), Michigan MSS: of 29 exposures in the first trimester, 4 newborns had major defects, 1 is expected (RR = 4.0; CI 95%: 1.0-10.2).

Carvedilol – C07AG02

It is available in Italy since 1993.

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

Studies on laboratory animals

- Gallery et al (1985): 95 healthy newborns exposed to oxprenolol, 9 of whom since the first trimester; 1 missed labor.

Feto-neonatal effects: there were no adverse outcomes in second-third trimester exposures (Gallery et al 1979 and 1985, Lubbe and Hodge 1981, Fidler et al 1983, Dommissie et al 1983).

C07 class conclusions: The studies we have been able to locate in literature do not highlight any population background reproductive risk following exposure to beta-blockers. This group of drugs has been widely studied and no teratogenic effects have been produced concerning either humans or laboratory animals. Manufacturer for registration has reported the same findings, but they are not available in databases. The use of beta-blockers in pregnancy is associated to possible neonatal effects (hypotension, respiratory depression, bradycardia, hypoglycemia and hyperbilirubinemia) which disappear within 48 hours. Due to such risks, the therapy with beta-blockers should be suspended 48-72 hours prior to birth. Exposed newborns must be monitored over the first 48-72 hours after birth. Possible low weight at birth should be noticed. In case of needs cardio-selective beta-blockers should be chosen, since they interfere less with uterine perfusion; besides, they should be used at dosages as low as possible, and anyway suspended 2-3 days prior to birth (Frishman and Chesner 1988).

C08 – Calcium antagonists

These drugs act blocking calcium channels in excitable cells. Many embryonic processes are calcium-dependent therefore the use of calcium antagonists in the first trimester of pregnancy might cause congenital anomalies or other adverse effects. Such a risk is only theoretical, though, since it is based on a study concerning frogs' embryos (Nurgess and Vere 1989), showing developmental anomalies after exposure to calcium antagonists.

Prospective cohort studies with internal controls

- Magee et al (1996), 6 TIS: 78 first trimester exposures to calcium antagonists (nifedipine 44%, verapamil 41%, diltiazem 13%, nimodipine 11%, felodipine 1%) alone or in association were matched to 78 controls. 2/66 congenital anomalies were reported among the exposures, vs. 0/72 among controls (p=0.22). The following defects were observed: multiple limb reduction defects in a newborn to diabetic ID mother, exposed to enalapril until the 10th week, then to diltiazem and hydralazine throughout pregnancy. Multiple defects (PS, hypospadias, digit thinning, inguinal hernia, and developmental delay) were noticed in a newborn to a mother with LES, exposed to nifedipine, carbamazepine, cyclophosphamide, prednisone, atenolol and ibuprofen. Reduced gestational age was observed: 37.5 ± 0.46 weeks among exposures, vs. 39.5±weeks among controls (p=0.02).

Outcome	Exposures	Controls
Live birth	64	72
Miscarriages	9	4
Induced abortion	6	5
Perinatal deaths	2	-
Congenital anomalies	2/66*	0/72

*See the text for the type of anomaly

C08C – Selective drugs with prevalent cardiovascular effect

Amlodipine – C08CA01

It is available in Italy since 1990.

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

Case report

- Rosbotham et al (1998): 1 newborn exposed throughout pregnancy had painful subcutaneous adiponecrosis, which disappeared in six months.

Studies on laboratory animals

- Horimoto et al (1991): nonteratogenic in rats, but there was a birth delay at doses 50 times higher than the maximum therapeutic dose in humans.

Felodipine – C08CA02

It is available in Italy since 1992.

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

Case report

- Casele et al (1997): 3 healthy newborns exposed to the drug throughout pregnancy.

Studies on laboratory animals

- Danielsson et al (1989, 1990): non fetotoxic or teratogenic in rats. Digit dose-dependent anomalies were noticed in rabbits (dosages from 0.4 to 4 times higher than the maximum therapeutic human dose).

Isradipine – C08CA03

This agent is structurally similar to nifedipine. It is 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.

Feto-neonatal effects: neonatal weight was not altered when the exposure was in the last month of pregnancy (Wide-Svensson et al 1995). There was a lack of adverse effects on utero-placental flow (Wide-Svensson et al 1990, Ingemarsson et al 1990, Lunell et al 1991, Feiks et al 1990 and 1991), and transitory hyperbilirubinemia was noticed (Lunell et al 1992).

Nicardipine – C08CA04

Nicardipine has a tocolytic action when used to treat premature birth menace (Jannet et al 1997). It is available in Italy since 1988.

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

Case report

- Alonso-Martinez and Pascual-Castroviejo (1999): 1 healthy newborn exposed throughout pregnancy.

Studies on laboratory animals

- Sato et al (1979): it is not fetotoxic or teratogenic in rats and rabbits at dosages 30-80 times higher than human therapeutic dose.
- Lirette et al (1987): reduced utero-placental flow in rabbits.
- Yoshida et al (1989): digit defects in rats.

Feto-neonatal effects: there were no adverse neonatal effects in exposures after the first trimester on cardiac rate and arterial pressure (Carbonne et al 1993, Matsuda et al 1994, Jannet et al 1994 and 1997, Ross et al 1998, Larmor et al 1999).

Nifedipine – C08CA05

It has a tocolytic action when used to treat premature birth menace (Papatsonis et al 2000). Patented in 1967.

Case report

- Valdes et al (2002): 1 healthy newborn exposed throughout pregnancy to nifedipine, apresoline, isosorbide and aspirin.

Retrospective cohort studies with internal controls

- Rosa (1993), Michigan MSS: of 37 exposed in the first trimester, 2 newborns had major defects, 2 are expected (RR = 1.0; CI 95%: 0.1-3.6).

Feto-neonatal effects: neither pressor maternal alterations, nor fetal frequency have been reported (Ulmsten et al 1980). There was neither alteration in neonatal bilirubin (Ferguson et al 1989), nor any adverse effect in

fetuses/newborns exposed after the first trimester (Ulmsten et al 1980 and 1984, Walters and Redman 1984, Read and Wellby 1986, Waisman et al 1989, Ferguson et al 1989 and 1990, Meyer et al 1990, Lurie et al 1990, Bracero et al 1991, Fenakel et al 1992, Murray et al 1992, Sibai et al 1992, Glock and Morales 1993, Roy and Pan 1993, Smith and Woodland 1993, Childress and Katz 1994, Tsatsaris et al 2002). Reduced growth and low neonatal weight was noticed (Constantine et al 1987).

Nimodipine – C08CA06

It is available in Italy since 1986.

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

Studies on laboratory animals

- Schluter (1986): nonteratogenic in rats or in rabbits, but developmental delay, embryo and intrauterine deaths increase, as well as peri- and post-natal mortality increase was observed at maternal toxic doses.

Feto-neonatal effects: there were no adverse effects in exposures after the first trimester (Belfort et al 1994).

Nisoldipine – C08CA07

It is available in Italy since 1991.

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

Nitrendipine – C08CA08

It is available in Italy since 1989.

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

Case report

- Colina-Chourio et al 1992): 1 healthy newborn exposed throughout pregnancy

Studies on laboratory animals

- Danielsson et al (1989, 1990): digit anomalies in rabbits.

Feto-neonatal effects: there were no adverse effects on exposures after the first trimester (Allen et al 1987).

Lacidipine – C08CA09

It is available in Italy since 1990.

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

Studies on laboratory animals

- Wada et al (1994): nonteratogenic in rabbits (18 mg/kg).

Manidipine – C08CA11

It is available in Italy since 1996.

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

Studies on laboratory animals

- Morseth and Ihara (1989): nonteratogenic in rats or in rabbits, but a growth delay at toxic doses has been noticed.

Lercanidipine – C08CA13

It is available in Italy since 1998.

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

C08D – Selective calcium antagonists with direct cardiac effect

C08DA – Phenyl-alkilamine derivatives

Verapamil – C08DA01

Patented in 1961.

Retrospective cohort studies with internal controls

- Rosa (1993), Michigan MSS: of 76 first trimester exposures, 1 newborn had major defects, 3 are expected (RR = 0,3; CI 95%: 0.0-1.9).

Feto-neonatal effects: This drug has been successfully used to treat fetal supraventricular tachycardia (Brittinger et al 1970, Lilja et al 1984, Klein and Repke 1984, Rey et al 1985, Maxwell et al 1988, Weiner et al 1988). Hypertrophic cardiomyopathy was reported in third trimester exposure (Shen et al 1995) as well as fetal death at 32 week, in a single exposure due to supraventricular tachycardia (Owen et al 1988) and neonatal reduced weight (Czeizel and Toth 1998). No adverse effects were noticed in 137 exposures after the first trimester (Orlandi et al 1986, Marlettini et al 1990).

Gallopamil – C08DA02

It is 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.

C08D8 – Benzothiazepine derivatives

Diltiazem – C08DB01

It is available in Italy since 1986.

Case report

- Lubbe (1987): 1 healthy newborn exposed since the first month throughout pregnancy to diltiazem and isosorbide.

Retrospective cohort studies with internal controls

- Rosa (1993), Michigan MSS: of 27 first trimester exposures, 4 newborns had major defects, 1 is expected, (RR = 4.0; CI 95%: 1.0-10.2). 2 of the newborns had a cardiovascular defect, 0.3 are expected (RR = 6.6; CI 95%: 0.8-24.1).

C08 class conclusions: The available studies, insufficient in some cases, do not reveal that first trimester exposure to calcium antagonists (mainly nifedipine) determine an increase in the population background reproductive risk. Some calcium antagonists, at higher dosages than for humans, have shown a

teratogenic action in laboratory animals, but none of the human congenital anomalies could be attributed to calcium antagonists. Diltiazem should deserve further research in order to give a better interpretation of the survey carried out by Rosa (1993) on the exceeding number of cardiovascular defects. The second and third trimester treatment has not revealed any particular adverse effects, which should rather be attributed to the background pathology.

These agents inhibit the enzyme converting angiotensin I in angiotensin II and affect kinins system (Linz et al 1995, Bonner 1997, Gainer et al 1998).

Case report

- Rosa and Bosco (1991): reconsidering an already published review (Rosa et al 1989) they have reported 29 cases of neonatal kidney failure in 18 exposed to enalapril, 9 to captopril and 2 to lisinopril.
- Muller and James (2002): 1 healthy newborn exposed to ACE-inhibitors until 24th week. An ultrasound scan had shown oligohydramnios, pericardial effusion, small bladder, and cranial deformity. The drug (unspecified) was suspended and 18 days later the anomalies revealed through ultrasound scan had receded.

Cohort studies without control

- Kreft-Jais et al (1988): of 31 exposures to ACE-inhibitors, 22 had been treated with captopril, 9 with enalapril.

Agent	Exposures & Period	Outcome (exposure period)
Captopril	6 throughout pregnancy 8 in the 1 st trimester 8 in the 2 nd &/or 3 rd trimester week)	7 healthy newborns (2 twins) 8 healthy newborns 2 stillbirths (25 th /29 th & 28 th 2 with patent ductus arteriosus (29/31 st and 32/35 th) 4 healthy newborns
Enalapril	1 throughout pregnancy 1 from 0 to 28 th week 6 in the 1 st trimester 1 from 24 to 26 th week	1 healthy newborn 1 healthy newborn 2 miscarriages 4 healthy newborns 1 stillbirth

- Piper et al (1992), Tennessee Medicaid: 19 newborns exposed to ACE-inhibitors, 12 cases in 1st and 7 cases in 3rd trimester. 1 newborn exposed in 1st trimester to captopril showing microcephaly and occipital encephalocele, out of 7; 1 newborn exposed to enalapril in the 3rd trimester had oligohydramnios, IUGR and anuria.
- Anonymous in MMWR (1997), ACEI Registry of spontaneous reports (1986-1994): 66 exposures to ACE-inhibitors in the first trimester. Miscarriage rate 23%. 48 newborns showing no evidence of tubular renal dysplasia, 1 newborn with persistent ductus arteriosus.
- Steffensem et al (1998), Danish Birth Registry: 21 healthy newborns exposed to ACE-inhibitors between 5 and 15 weeks of gestation.

Feto-neonatal effects: hypoglycemia (Moore et al 1997).

Captopril – C09AA01 – C09ABA01

It is available in Italy since 1981.

Case report

- Duminy and Burger (1981): single fetus exposed to captopril, propranolol, and amiloride showing hypoplasia of the left lower limb and anomalous cranial bone formation.
- Guignard et al (1981): 1 newborn exposed between 26 to the 28 weeks of pregnancy showing oligohydramnios, hypotension, respiratory distress, and anuria died 7 days later.

- Broughton-Pipkin et al (1982): 1 newborn exposed at 28 week of gestation died on day 8 due to renal impairment.
- Boutroy et al (1984): 1 newborn exposed throughout pregnancy to captopril and acebutolol showing IURG, bradycardia, hypotension, respiratory arrest and patent ductus arteriosus.
- Rothberg and Lorez (1984): 1 newborn exposed throughout pregnancy to captopril, methyldopa and furosemide, showing oligohydramnios, IUGR, pulmonary hypoplasia, hypoplasia of cranial bones, contracture of the extremities, hypotension, and anuria, died at one month of age.
- Kaler et al (1987): 1 newborn exposed throughout pregnancy to captopril, minoxidil and propranolol showing multiple malformations (onhalocele, hypertrichosis, flat nasal bridge, low-positioned ears, microtia, clinodactyly, cryptorchidism, DIV and cerebral defect).
- Hurault de Ligny et al (1987): 1 newborn exposed between 32 and 35 weeks of gestation showing persistent ductus arteriosus.
- Barr (1990): 1 newborn exposed throughout pregnancy to captopril, prednisone, atenolol and furosemide, showing oligohydramnios, IUGR and low ossification of the cranial bone.
- Barr and Cohen (1991): 1 newborn exposed to prednisolone, atenolol, furosemide and captopril showing renal tubular dysgenesis and low ossification of the cranial bone, died 14 hours later.
- Lenoir et al (1994): 1 exposed newborn showing renal failure.
- Sadeck et al (1997): 1 newborn exposed in the second half of pregnancy showing acute renal failure and patent ductus arteriosus.

Cohort studies without control

- Burrows and Burrows (1998): 9 healthy newborns exposed in the first trimester
- Easterling et al (2000): 10 healthy newborns exposed to low doses of captopril in the second or third trimester

Retrospective cohort studies with internal controls

- Rosa (1993), Michigan MSS: of 86 first trimester exposures, 4 newborns had major defects, 3 are expected. RR = 1.3 (CI 95%: 0.4-3.4).

Enalapril – C09AA02- C09ABA02

It is available in Italy since 1987.

Case report

- Schubiger et al (1998): 1 newborn exposed at 32 week of gestation had acute renal failure.
- Metha and Modi (1989): 1 newborn exposed throughout pregnancy to enalapril, azathioprine, atenolol and prednisolone had IUGR, oligohydramnios, hypotension, anuria, contracture of the extremities, pulmonary hypoplasia and low ossification of the cranial bone.
- Smith (1989): 4 pregnancies of the same woman were studied: 1 exposure to captopril (see), and 3 exposures starting prior to pregnancy to enalapril, atenolol and nifedipine giving 1 stillbirth (18th week of gestation) and 2 healthy newborns.
- Broughton-Pipkin et al (1989): 1 healthy newborn exposed between 15 to the 20 weeks of gestation. Oliguresis was noticed at 20 weeks, but it receded when the drug was suspended.
- Scott and Purohit (1989): 1 newborn exposed to enalapril and other hypertensives throughout pregnancy had anuria.
- Hulton et al (1990): 1 newborn exposed in the third trimester had oligohydramnios and renal failure.

- Cunniff et al (1990): 1 newborn exposed throughout pregnancy to enalapril, propranolol and hydrochlorothiazide, had oligohydramnios, renal impairment, low ossification of cranial bones, short limbs, renal tubular dysplasia, hypotension and anuria, died of renal failure.
- Thorpe-Beeston et al (1993): 1 newborn exposed throughout pregnancy to enalapril and furosemide had oligohydramnios, polycystic kidney and bilateral clubfoot, died soon after birth.
- Rhabbour et al (1994): 1 newborn exposed throughout pregnancy had oligohydramnios, respiratory distress, hypotension, anuria, and generalized edema.
- Lavoratti et al (1997): 1 newborn exposed in the second half of pregnancy had neonatal anuria.
- Magee (1998): 1 newborn exposed to enalapril in the first 10 weeks, then to diltiazem and hydralazine until birth, had limbs reduction defects (aplasia of upper limbs, hypoplasia of lower left limb, hypodactyly and adactyly of the right foot). The mother suffered from insulin-dependent diabetes.
- Tabacova et al (2003): 110 cases reported to FDA were surveyed and the previously recorded comments were confirmed.
- Prasad et al (2003): 1 newborn exposed throughout pregnancy had oligohydramnios, low ossification of cranial bones and bilateral clubfoot.

Cohort studies without control

- Lip et al (1997): 10 healthy newborns, 8 of whom had been exposed in the first trimester and the other 2 exposed at 14 and 15 weeks of gestation, respectively.

Retrospective cohort studies with internal controls

- Rosa (1993), Michigan MSS: of 40 first trimester exposures, 4 newborns had major defects, 2 are expected. RR = 2.0 (CI 95%: 0.5-5.1).

Lisinopril – C09AA03 – C09ABA03

It is available in Italy since 1992.

Case report

- Barr and Cohen (1991): 1 newborn exposed throughout pregnancy to lisinopril, with tubular renal dysgenesis and low ossification of cranial bones.
- Pryde et al (1992): 1 newborn exposed throughout pregnancy showing IUGR, low ossification of cranial bones, tubular renal dysgenesis, hypotension and anuria.
- Bhatt-Mehta and Deluga (1993): 1 newborn exposed throughout pregnancy showing low ossification of cranial bones and anuria.
- Burrows and Burrows (1998) and Yip et al (1998): 3 healthy newborns exposed to this drug during pregnancy.
- Tomlinson et al (2000): 1 newborn exposed after the 20th week of gestation showing renal failure and neonatal necrotizing enterocolitis.

Cohort studies without controls

- Lip et al (1997): of 6 healthy newborns, 4 had been exposed throughout the first trimester and 2 until week 20 and 25 of gestation, respectively.

Retrospective cohort studies with internal controls

- Rosa (1993), Michigan MSS: of 15 first trimester exposures, 2 newborns had major defects, 0.6 are expected. RR = 3.3 (CI 95%: 0.4-12.0).

Perindopril – C09AA04 –C09ABA04

It is available in Italy since 1992.

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

Studies on laboratory animals

- Harada et al (1994): nonteratogenic in rats (16 mg/kg) or in rabbits (10 mg/kg).

Ramipril – C09AA05 – C09ABA05

It is available in Italy since 1990.

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

Quinapril – C09AA06 – C09ABA06

It is available in Italy since 1989.

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

Studies on laboratory animals

- Imanishi et al (1993): nonteratogenic in rats (100 mg/kg).
- Yoneyama et al (1995): nonteratogenic in rabbits (100 mg/kg).
- Imanishi et al (1995): nonteratogenic in rats (3mg/kg), but showing a reduction in neonatal weight. No behavioral alterations have been noticed, anyway.

Benazepril – C09AA07 – C09ABA07

It is available in Italy since 1991.

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

Case report

- Chisholm et al (1997): 1 healthy newborn exposed until 27 weeks, had oligohydramnios that receded when the drug was suspended.
- Tareen et al (2001): 1 newborn exposed throughout pregnancy had low ossification of cranial bones, renal failure and neurological compliance.

Studies on laboratory animals

- Takahashi (1991): renal pelvis and urethra dilatation in rats (1,000 mg/kg).

Cilazapril – C09AA08 – C09ABA08

It is 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.

Fosinopril – C09AA09 – C09ABA09

It is available in Italy since 1992.

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

Studies on laboratory animals

- Grove et al (1995): cranial ossification in rats (16 mg/kg)

Trandolapril – C09AA10 – C09BB10

It is available in Italy since 1996.

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

Studies on laboratory animals

- Matsuura et al (1993): nonteratogenic in rats (30/300 mg/kg)

Spirapril – C09AA11

It is available in Italy since 1997.

Delapril – C09AA12 –C09ABA12

It is available in Italy since 1995.

Moexipril – C09AA13

It is available in Italy since 1999.

Zofenopril – C09AA15

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.

C09AA class conclusions: The use of ACE-inhibitors during the second and third trimester of pregnancy has clearly shown adverse effects on fetal growth. Fetopathy is mainly characterized by tubular renal dysplasia, causing oligohydramnios and anuria (with possible after-effects due to hypokinesia, such as limb defects, facial dysmorphism, articular anomalies and pulmonary hypoplasia), associated with growth retardation of skull bones, patent ductus arteriosus and IUGR. Such anomalies can be caused by fetal hypotension, following the ACE-inhibitors action (MMWR 1997). Late fetal mortality and neonatal mortality are frequent. Week 26 is shown to be the most critical one (Buttar 1997). The outcome appears to be progressive nonetheless a prompt interruption of the drug seems to be able to make oligohydramnios recede, but not the renal injury.

A precise risk estimate is impossible: from the survey of several exposed newborns it appears to be rare (1-5%). The available data on ACE-inhibitors do not suggest any adverse outcomes on embryo development due to exposures, when limited at the first trimester of pregnancy.

C09C –Angiotensin II Antagonists

They mostly act through the selective blockage of angiotensin I receptors, reducing the pressor effects of angiotensin II. They are pharmacologically similar to ACE-inhibitors.

Losartan – C09CA01

It is available in Italy since 1995.

Case report

- Mann et al (1999): 3 pregnancies exposed during the first 6-8 weeks of gestation. 1 spontaneous abortion, 1 healthy newborn, 1 premature infant (29th week) who died 9 days after birth.
- Martinovic et al (2001): 1 exposure throughout pregnancy caused neonatal death with oligohydramnios, muscular hypotonia, persistent anuria, and hypoplasia of skull bones and limbs.

- Lambot et al (2001): 1 healthy newborn exposed throughout pregnancy and showing oligohydramnios, low neonatal weight, respiratory distress, anuria, limb defects, facial dysmorphism (Potter) and patent ductus arteriosus, died on day 4.
- Saji et al (2001): 1 exposure from 17 to 31st week caused fetal death having oligohydramnios, pulmonary hypoplasia and hypoplasia of limbs and skull bones.

Eprosartan – C09CA02

It is available in Italy since 2000.

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

Valsartan – C09CA03

It is available in Italy since 1998.

Case report

- Chung et al (2001): 3 healthy newborns exposed since conception until week 7, 10 and 19 of pregnancy, respectively.
- Martinovic et al (2001): after exposure to valsartan and hydrochlorothiazide throughout pregnancy the fetus died on week 32 with anhydramnios, dilatation of cerebral ventricles, thoracic hypoplasia and renal hypoeogenicity. In another case of exposure to valsartan, hydrochlorothiazide and metformin throughout pregnancy the fetus died on week 27 with anhydramnios.
- Briggs and Nageotte (2001): 1 exposure until the 24th week to valsartan and atenolol caused fetal death at 33 weeks with anhydramnios and pulmonary hypoplasia.
- Biswa et al (2002): of 4 pregnancies exposed to valsartan in the first trimester, 2 were spontaneous abortions, 1 VIP and 1 healthy newborn.

Irbesartan – C09CA06

It is available in Italy since 1998.

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

Candesartan – C09CA06

It is available in Italy since 1998.

Case report

- Hinsberger et al (2001): 1 newborn exposed throughout pregnancy showing transitory anuria and hemifacial (right) and plexus paralysis.
- Cox et al (2003): 1 exposure throughout pregnancy with renal monolateral agenesis, hypospadias and other malformations.

Studies on laboratory animals

- Ooshima et al (1996) late renal injury in fetuses and newborns of rats, mice and rabbits.

Telmisartan – C09CA07

It is 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.

Case report

- Pietrement et al (2003): 1 newborn exposed after the first trimester with transitory acute renal insufficiency.

C09CA class conclusions: Recorded clinical reports have shown exposure to Angiotensin II Antagonists during the second and third trimesters can alter fetal renal function and provoke consequent damages, just like ACE-inhibitors (see).

C10A – Hypocholesterolemic and Triglyceride-reducing agents

Agents used in the treatment of hyperlipidemia are of different type: inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA); lipid-lowering agents; ion-exchange resins and nicotinic acid. A therapy aiming at lowering lipids should necessarily consider that during pregnancy cholesterol and its biosynthesis products are of primary importance for the development of the fetus (steroid synthesis, cell membranes).

C10AA – Inhibitors of HMG-CoA reductase

These are at present the most used lipid-lowering agents. Their activity blocks HMG-CoA reductase enzyme that catalyzes the synthesis of cholesterol.

Simvastatin – C10AA01

This statin is available in Italy since 1990.

Case report

- Lemoine et al (2001): 1 newborn exposed in the first trimester showing stenosis of the right pielo-ureteral junction.

Prospective cohort studies without controls

- Manson et al (1966), Manufacturer, spontaneous reports register: of 126 exposures, 40 VIP, 13 (15%) spontaneous abortions, 1 (1.2%) fetal deaths and/or stillbirths, 3 (3.5%) adverse outcomes in premature births (patent ductus arteriosus, respiratory distress, bilateral hydrocele and hyperbilirubinemia), 64 (74,4%) healthy newborns, 5 newborns with congenital anomalies (cleft lip and cleft palate, clubfoot, multiple malformations in one twin, trisomy 18 syndrome, polydactyly, hypospadias). Neither polydactyly nor hypospadias can be attributed to this medication, because the exposure has not occurred in the critical period; not even trisomy 18 can be attributed to this medication. All of the above mentioned cases should be evaluated with caution, since they were based on spontaneous uncontrolled reports.
- Freyssinges and Ducrocq (1966), Manufacturer: the records published by Manson et al (1996) have been reviewed without substantially adding any further information.

Pravastatin – C10AA03

This statin is available in Italy since 1990.

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

Fluvastatin – C10AA04

This statin is available in Italy since 1995.

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

Case report

- Seguin and Samuels (1999): 1 healthy newborn exposed in the first 9 weeks of pregnancy to fluvastatin, prednisone, cyclosporin, azathioprine, cefalexin and ranitidine.

Studies on laboratory animals

- Kazuyoshi et al (1995): nonteratogenic in rats (36 mg/kg per os).

Atorvastatin – C10AA05

This statin has a high molecular weight (around 1,161) suggesting that it does not cross the placenta. It is available in Italy since 1997.

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

Case report

- Vagt and Kastendieck (2000): 1 newborn with hypo-agenesia of upper limbs had been exposed from conception to the 7th week.

Studies on laboratory animals

- Dostal et al (1994): nonteratogenic in rats up to 300 mg/kg and in rabbits up to 30 mg/kg.

C10AA class conclusions: There is no written evidence, otherwise incomplete, of specific studies concerning the use of the different agents in this therapeutic group during human pregnancy. HMG-CoA-reductase inhibitors are contraindicated during gestation, since cholesterol and the products of its biosynthesis are of fundamental importance in fetal development and their decrease might give rise to some risk. Inadvertent exposure to simvastatin during the first trimester appears unlikely to increase the risk of adverse pregnancy outcome.

C10AB – Antilipidemic agents (Fibrates)

Bezafibrate – C10AB02

Patented in 1971.

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

Studies on laboratory animals

- Naitoh et al (1988): nonteratogenic in rats (800 mg/kg).

Gemfibrozil – C10AB04

It is available in Italy since 1985.

Case report

- Jaber et al (1992): 1 healthy newborn exposed in the first trimester for 2 months.

Retrospective cohort studies with internal controls

- Rosa (1993), Michigan MSS: none of the 8 newborns exposed in the first trimester was showing major defects.

Fenofibrate – C10AB05

Patented in 1971

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

Studies on laboratory animals

- Ujhazy et al (1989): nonteratogenic in mice (585 mg/kg).
- Kobayashi et al (1995): nonteratogenic in rats (200 mg/kg).
- Noguchi et al (1995): nonteratogenic in rats (100 mg/kg).

C10AB class conclusions: There is no written evidence of specific studies concerning the use of drugs in this therapeutic group during human pregnancy. In case of exposure, the following issues should be considered: absence of reported anomalies over the long period of commercialization, although a limited use in pregnancy is likely, and lack of teratogenic effects in laboratory animals.

C10AC – Bile acids binders

These agents are not absorbed in the systemic circulation and do not have systemic effects (Goodman and Gilman 2001).

Cholestyramine – C10AC01

This is an anion exchange resin that impedes the absorption of fat-soluble vitamins. Patented in 1968.

Retrospective cohort studies with internal controls

- Rosa (1993), Michigan MSS: none of the 4 newborns exposed in the first trimester was showing major defects.

Studies on laboratory animals

- Koda et al (1982 a, b): nonteratogenic in rats or in rabbits.

Feto-neonatal effects: no adverse outcomes on the fetus/newborn exposed after the first trimester of gestation for the treatment of hepatic cholestasis (Lutz and Margolis 1969, Heikkinen et al 1982, Shaw et al 1982, Fedorkow et al 1989, Shorr-Lesnicks et al 1991). One newborn exposed after the first trimester has been described with subdural hematoma, hydrocephaly, hepatomegaly and bilateral pleural effusion.

Detastrano – C101C03

It is a destano derivative water-soluble polycation. It is available in Italy since 1978.

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.

C10AC03 class conclusions: There is no written evidence of specific studies concerning the use of drugs in this therapeutic group during human pregnancy. In case of exposure, the following should be considered: lack of systemic absorption, absence of reported anomalies over the long period of commercialization – although a limited use in pregnancy is likely, and lack of teratogenic effects in laboratory animals.

C10AD – Nicotinic Acid and its derivatives

Acipimox – C10AD06

This hypolipidemic, analogue of nicotinic acid (agent with vitamin PP activity) is a lipolysis inhibitor. Patented in 1972.

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 acipimox during human pregnancy. In case of exposure, the following should be considered: its analogy with vitamin PP, absence of reported anomalies over the long period of commercialization - although a limited use in pregnancy is likely - and lack of teratogenic effects in laboratory animals.

C10AX - More Hypocholesterolemic and Triglyceride-reducing agents

Benfluorex – C10AX04

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.

Meglutol – C10AX05

Patented in 1971.

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

Studies on laboratory animals

Savoie and Lupien (1975): nonteratogenic in rats (500 mg/kg) and in mice (3.7 g/kg per os and 1.6g/kg intramuscular).

Omega-3-Triglycerides – C10AX06

These are ethyl esters of polyunsaturated fatty acids omega 3 (EPA, DHA and α -tocopherol). They are available in Italy since 1991.

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

Feto-neonatal effects: Their use late in pregnancy might induce a risk of preterm delivery and there are no adverse effects on newborns (Olsen et al 2003), but there are no positive outcomes on maternal hypertension or on the intrauterine growth retardation (Olsen et al 1992, Onwude et al 1995).

Phosphatidylcholine – C10AX49

It is available in Italy since 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.

C10AX class conclusions: There is no written evidence of specific studies concerning the use of drugs in this therapeutic group during human pregnancy. In case of exposure, the following should be considered: physiologic characteristics of some agents, absence of reported anomalies over the long period of commercialization – although a limited use in pregnancy is likely, and lack of teratogenic effects in laboratory animals.