

B – BLOOD AND HEMOPOIETIC ORGAN

B01A – Antithrombotic drugs

B01AA – Vitamin K antagonists

Warfarin – BB01AA03

This is an anticoagulant and a coumarin agent. It inhibits the synthesis of vitamin K-dependent factors. Patented in 1947

Systematic reviews

- Chan et al (2000): 28 cohort studies of different size were analyzed. (Palacios-Macedo et al 1969, Ibarra-Perez et al 1972, Casanegra et al 1975, Ibarra-Perez et al 1976, Limet and Gordin 1977, Lutz et 1978, Chen et al 1982, O'Neil et al 1982, Larrea et al 1983, Wang et al 1983, Guidozzi 1984, Javares et al 1984, Salazar et al 1984, Matorras et al 1985, Ben Ismail et al 1986, Iturbe-Alessio et al 1986, Lee et al 1986, Pajszczyk-Kieszkiwicz et al 1986, Vitali et al 1986, Pavankumar et al 1988, Sraeli et al 1989, Ayhan et al 1991, Cotrufo et al 1991, Born et al 1992, Caruso et al 1994, Lee et al 1994, Lecuru et al 1996, Salazar et al 1996). The percentage of spontaneous abortions following exposures to oral anticoagulant agents was of 24.7% (CI 18.5-29.6); there was a percentage of 6.4% (CI 4.6-8.9) congenital anomalies and 33.6% (CI 25.4-40.1) of intrauterine death in exposures throughout pregnancy. 41 newborns had congenital anomalies, 29 revealed symptoms of warfarin embryopathy, 4 had central nervous system defects, 4 had facial schisis, 4 presented different defects (single kidney + finger anomaly; hypoplasia of the left ventricle; corneal spot and bilateral hand polydactyly). The analysis of the prospective studies only gave the following findings: percentage of miscarriages in exposures to oral anticoagulant agents = 21% (CI 16.3-26.8), congenital anomalies among exposures throughout pregnancy = 10.2% (CI 5.9-16.8), intrauterine death = 29.7% (CI 14.4-39.7).

Incidence and main outcomes in pregnancies exposed to anticoagulants (mostly warfarin) (% and CI 95%)

Trimestral treatment	Miscarriages	Congenital anomalies	Intrauterine death
Anticoagulants 1 st -2 nd -3 rd	169/792 (24.7%, 18.5-29.6)	35/549 (6.4%, 4.6-8.9)	266/792 (33.6%, 25.4-40.1)
Eparine 1 st	57/230	6/174	61/230
Anticoagulants 2 nd , 3 rd	(24.8%, 13.6-41.8)	(3.4%, 1.4-7.7)	(26.5%, 16.7-42.5)
Eparine 1 st -2 nd -3 rd	5/21 (23.8%, 9.2-47.4)	0/17 *(0.0-19.5)	9/21 (42.9%, 22.7-65.5)
No anticoagulant Treatment	10/102 (9.8%, 5.1-17.7)	3/92 (3.3%, 0.9-9.9)	20/102 (19.6%, 12.7-28.9)
Anticoagulants 1 st , 2 nd , 3 rd	52/247 (21.1%, 16.3-26.8)	14/137 (10.2%, 5.9-16.8)	73/246 (29.7%, 14.4-39.7)
Heparin 1 st , Anticoagulants 2 nd , 3 rd	38/182 (20.9%, 11.8-35.9)	4/141 (2.8%, 0.9-7.5)	41/182 (22.5%, 13.6-38.1)

Review of cases and of small cohort studies

- Hall (1976 a,b,), Pauli and Hall (1979), and Hall et al (1980): literature review of 418 papers published from 1945 to 1979 or personally mentioned by the authors. This review has been the first to set out the characteristics of the exposure to coumarins. All of the 24 patients presenting warfarin embryopathy had been exposed between 6 and 9 weeks of pregnancy.

Total exposures	418		
Miscarriages	36	CNS defects	6
Total newborns	350	Normal premature	8
No-problems newborns	293	Premature deaths	4
Hemorrhage newborns	7	Premature with hemorrhage	4
Warfarin embryopathy	11	Other neonatal problems	12
Warfarin embryopathy + CNS effects	5	Stillbirths	32

- Kleinebrecht (1982): This further review completes, with 471 exposures to coumarins, without substantially changing Hall's outcomes.
- Schardein (2000): literature review of 73 cases of coumarins embryopathy to set out the clinical picture (see conclusions)

Case report (other defects)

- There are many other warfarin embryopathy reports, as well as a large range of reports concerning defects due to exposures in the 2nd and 3rd trimester, such as: asplenia, cardiopathy, (Brambel et al 1951); anencephaly, spina bifida, absence of clavicles and cardiopathy (Brambel et al 1951); cardiopathy (Aaro and Juergens 1971); multiple not specified malformations (Oakley and Doherty 1976); asplenia, cardiopathy, intestinal malrotation, fingers and nails hypoplasia (Cox et al 1957); eye malformations (Baillie et al 1980), renal and digit anomalies (Hall et al 1980); single kidney, feet defects (Lutz et al 1980); cardiovascular and lung malformations (Dean et al 1981); eye defects, scoliosis (Hill and Tennyson 1984); diaphragmatic hernia (O'Donnell et al 1985); corneal opacity and microphthalmia, epilepsy, congenital scoliosis and talipes equinovarus (Kaplan 1985); micrognathia, microglossia digit and nails hypoplasia (Ruthnum and Tolmie 1987), Fallot teratology (Balde et al 1988); macrofallus, mandibular hypoplasia, clubfoot, renal agenesis and hypoplasia (Hall 1989), diaphragmatic hernia and lung hypoplasia (Normann and Stray-Pedersen 1989); schiz-encephaly (Pati and Helmbrecht 1994). None of these do modify, anyway, the acquired knowledge in the reviews mentioned above.
- Many more (about 200) reports are also available in literature, concerning healthy exposed newborns (Holzgreve et al 1976, Ibarra-Perez et al 1976, Russo et al 1979, Solomon and Brent 1980, Kort and Cassel 1981, Dean et al 1981, Chen et al 1982, Chong et al 1984, Salazar et al 1984, Hill and Tennyson 1984, Cotrufo et al 1991).
- Moe (1982) reported 5 exposures at the beginning and at middle second trimester showing no embryopathies.

Cohort retrospective studies without controls (not included in the systematic review by Chan et al 2000)

- Kort and Cassel (1981): 41 exposures to warfarin (28 since first trimester) until 36th-38th week, then substituted with heparin. Out of 36 newborns, 3 (8.3%) had congenital anomalies (labio-cleft palate, meningomyelocele, bilateral hip dislocation). Fetal mortality 12.5%.

- Chong et al (1984): 22 children exposed in pregnancy and controlled around 4 years of age revealed a normal psychophysical growth.
- Wong et al (1993): Of 29 newborns exposed to warfarin, 11 were healthy newborns, 12 had warfarin embryopathies and there was one intraventricular hemorrhage.

Acenocoumarol – B01AA07

This is an antithrombotic, antagonist of vitamin k, coumarin derivative. As a coumarin derivative it interferes with the hepatic synthesis of vitamin-k dependent coagulation factors. Patented in 1950.

Case report

- Casanegra et al (1975): 1 exposure showing polydactyly.
- Bony et al (2002): 1 exposure showing warfarin embryopathy.

Cohort studies without controls

- Olwin and Koppel (1969): 16 healthy newborns exposed throughout pregnancy

Retrospective cohort studies with external controls

- Wesseling et al (2001): children aged 7-15, were investigated. 306 had been exposed to coumarins (acenocoumarol and phenprocoumon), 267 controls. OR for mild neurological disorders (IQ<80) following exposure to coumarins = 1.9 (CI 95%: 1.1-3.4); following exposure in the second and third trimesters OR = 2.1 (CI 95%: 1.2-3.8).

Prospective cohort studies with internal controls

- Larrea et al (1983): 47 exposures, 102,126 controls. There were 23.4% spontaneous abortions among cases, vs. 15% among controls. Prematurity: 22.2% vs. 4.3. Of 36 exposed newborns, 2 (5.5%) had pointed chondrodysplasia, 1 also presented mental retardation.
- Salazar et al (1984): 68 pregnancies exposed to acenocoumarol in the first trimester (later substituted with heparin); 128 treated since week 38. Warfarin embryopathy in 7.9% of the second group of newborns.
- Iturbe-Alessio et al (1986): 72 exposures: 23 in weeks 0-6 and 13-38, 12 in weeks 0-7 and 12-38, 37 in weeks 0-38. 54 newborns, 10 of whom (5.5%) showing elements of warfarin embryopathy.

B01AA class conclusions: It is set out that there exists 2 well distinguished associated defects to the use of coumarins in pregnancy, related to the period of exposure. The characteristic warfarin or, we should say coumarin embryopathy takes place following early exposure in the first trimester. Fetal death and other defects, especially those involving the central nervous system, appear following a later exposure, usually in the second or third trimester. Warfarin embryopathy is mainly characterized by:

- a. ossification defect of nasal bone, ranging from a less prominent nasal sella to a complete aplasia, with a sunken nose;
- b. epiphyseal dysplasia, mainly in lumbosacral tract of axial skeleton, as well as of thigh bone and heel bone;
- c. hydrocephaly, microcephaly, Dandy-Walker anomaly, dorsal median-line dysplasia (agenesia of corpus callosum, cerebral and cerebellar atrophy), dysplasia of ventral median line (eye- atrophy) or mental retardation alone.

Skeleton diseases appear to be a constant element in every reported case and associated to a pre-birth exposure between 6 and 9 weeks. Central nervous system disorders, reported in about half of the cases, seem to be associated to all-over pregnancy exposure, especially in the second and third trimester. These

disorders are very probably determined by hemorrhages (Warkany and Bofinger 1975).

Here are more appearances of coumarin syndrome:

- a. neonatal weight lower than tenth percentile (40%);
- b. eye diseases (23%)
- c. rhizomelic hypoplasia of ends or finger hypoplasia (50%)

The teratogenic risk currently attributable to warfarin is of 5-10% (Chan et al 2000: 6.4-10.2%). The universally accepted protocols by Harrison and Roschke (1975) and by Bonnar (1977) propose to use heparin up to week 12 (although this is very likely to cause miscarriage). Then substitute it with warfarin up to week 36 or until 2-3 weeks before assumed birth-date (Maternal Neonatal Haemostasis Working Party of the Haemostasis Thrombosis Task 1993).

B01AB – Heparin drugs

Standard heparin is a mixed of molecules having different molecular weight (around 16,000 daltons), they do not cross placenta and if they do it is only at a very low percentage. Also low molecular weight heparin do not cross the placenta, since their weight is around 4,200-4,500 daltons.

Systematic review

- Ensom and Stephenson (1999): 40 studies have been analyzed, different in quality, reporting the use of heparin in the treatment, above all, of thromboprophylaxis during pregnancy. They were chosen in a total of 728 pregnancies, 340 (47%) of which exposed to dalteparin, 192 (26%) to enoxaparin, 108 (15%) to certoparin, 54 (7%) to nadroparin, 30 (4%) to other low weight heparins and 6 (<1%) to non specified heparins. The review points out that the treatment with heparin or its derivatives is effective for mothers and harmless for offspring.

Heparin – B01AB01

It does not cross the placenta. It is available in Italy since 1951. Long term treatments with heparin at dosages higher than 20,000 U/day for over 4 months may cause maternal osteoporosis.

Dalteparin – B01AB04

This has low molecular weight (3,000-8,000 daltons). It does not cross the placenta (Melissari et al 1992; Wahlberg et al 1994). Available since 1989.

Enoxaparin – B01AB05

This has low molecular weight (4,300 daltons). It does not cross the placenta (Dimitrakakis et al 2000). Available since 1985.

Retrospective cohort studies without controls

- Lepercq (2001): of 693 exposed newborns, 17 (2.5%) had major defects and 10 (1.4%) had severe neonatal hemorrhages.

Nadroparin – B01AB06

This heparin has low molecular weight (4,300 daltons). It appears not to cross the placenta and it is available in Italy since 1995.

Parnaparin – B01AB07

This heparin has low molecular weight (average 4,500 daltons). It appears not to cross the placenta and it is available in Italy since 1993.

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

Reviparin – B01AB08

This heparin has a low molecular weight (3,500-4,500 daltons). A breakdown sodium product of **porcina??** intestinal mucosa in water solution. It appears not to cross the placenta. Available since 1995.

Cohort studies without controls

- Laskin et al (1997): 35 healthy newborns exposed throughout pregnancy.

Sulodexide – B01AB11

It is a fibrinolytic anti-platelet agent, 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.

B01AB class conclusions: In consideration of the available data in current literature there appears to be no evidence that the use of heparin drugs in the first trimester of pregnancy be associated with a quantifiable population background reproductive risk. The increased number of miscarriages, stillbirths and premature births reported in some studies is very probably to be attributed to maternal pathology. The frequency of maternal hemorrhages is of 10%. Long term treatments with heparin at dosages higher than 20,000 U/die for over 4 months may cause maternal osteoporosis.

B01AB49 – Various drugs

Heparan sulfate

It is an anti-thrombosis, glycosaminoglycan, 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.

Glucuro-sulfoglycan glucoronilglucosaminglycan sulfate

It is an anti-thrombosis, it inhibits the activated coagulation factor (10th), it lowers hematic viscosity and has a fibrinolytic action. 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.

Mesoglican

Heparinoid of extractive origin, it is an antiplatelet agent, a complex of natural glucosaminoglycans (GAG). 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.

Pentosan

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.

Sulfo-mucopolysaccharide

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.

B01AB49 class conclusions: There is no written evidence of specific studies concerning the use of drugs in this therapeutic class during human pregnancy. Nevertheless, in consideration of the lack of reported anomalies over the period of commercialization as well as of teratogenic action on laboratory animals (records provided by manufacturer for registration, not available in databases), in case of exposure an increase in the population background reproductive risk is not likely.

B01AC – Antiplatelet drugs

These are used to prevent thrombosis caused by platelet adhesiveness, that create the starting hemostatic plug in vascular lesions.

Chloricromen – B01AC02

This synthetic coumarin derivative inhibits thromboxane and increases the production of vessel prostacyclin. 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.

Conclusions: Their chemical similarities with coumarins recommend not using these drugs in pregnancy. See warfarin.

Picotamid – B01AC03

It inhibits the synthesis of thromboxane A and stops platelet receptors. 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.

Clopidogrel B01AC04

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.

Feto-neonatal effects: No adverse outcomes have been reported in newborns exposed in the second half of pregnancy due to maternal infarct (Klinzing et al 2001).

Ticlopidine – B01AC05

This agent lowers the platelet adhesiveness and inhibits platelet aggregation. Available in Italy since 1981.

No specific studies have been located in literature consistent with its use in human pregnancy.

Case report

- Ueno et al (2001): 1 exposure since the beginning of week 36 to ticlopidine, dipiridamole and aspirin.

Studies on laboratory animals

- Watanabe et al (1980): nonteratogenic in rats (320 mg/kg/die gavage), in some cases a delay in fetus ossification has been noticed.

Feto-neonatal effects: No adverse effects on a newborn exposed in the second half of pregnancy, due to maternal infarct (Sebastian et al 1988).

Dipyridamole – B01AC07

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.

Case report

- Ueno et al (2001): 1 healthy newborn exposed since the beginning of week 36 to ticlopidine, dipyridamole and aspirin.

Feto-neonatal effects: No adverse effects have been reported in newborns exposed in the second half of pregnancy (Ahmad et al 1976, Ibarra and Perez 1976). Benefits deriving from the use of dipyridamole to prevent pre-eclampsism have not been yet thoroughly evaluated (Knight et al 2004).

Indobufen – B01AC01

This is a fenilbutirric derivative. Patented in 1970.

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

Triflusal – B01AC18

It is a strong inhibitor of platelet aggregation, also having a remarkable antithrombotic activity; it is orally active. 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.

Sulfinpirazone – B01AC49

The anti-aggregation action persists beyond the period of its circulation in plasma. 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.

B01AX – More antithrombotic drugs

Defibrotide – B01AX01

It is an antithrombotic, fibrinolytic agent. 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.

B01AC and B01AX class conclusions: There are limited studies or no written evidence at all of specific studies concerning the use in human pregnancy of drugs in these therapeutic groups. In case of exposure – except for chloricromen - an increase in the background reproductive risk is not likely, due to a lack of reported anomalies over the long period of commercialization. Besides, teratogenic effects in laboratory animals have not been found (records provided by manufacturer for registration, not available in databases).

B02 – Anti-hemorrhagic drugs

B02A – Anti-fibrinolytic drugs

B02AA – Amino acids

Amino-caproic acid – B02AAA01

This is a plasmin non-activator drug. Available in Italy since 1975.

Clinic reports

- Ziliacus (1966): 4 healthy newborns exposed in the first trimester.

Feto-neonatal effects: Different reports are available concerning exposures in the second half of pregnancy with no adverse outcomes for the mother or the newborn (Onnis et al 1983, Willoughby 1984).

Tranexamic acid – B02AA02

Available in Italy since 1970.

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

Feto-neonatal effects: The different studies carried out after embryonic life, have not uncovered unwilling outcomes either in fetal growth or in the newborn and in the pregnant (Briggs et al 2002).

B02AA class conclusion: There are limited studies or no written evidence at all of specific studies concerning the use in human pregnancy of drugs in this therapeutic group. 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).

B02BA – Vitamin K

Phytomenadione (vitamin K1) – B02BA01

Menadiol (vitamin K3) – B02BA49

There is no need for extra vitamin k in pregnancy. This is recommendable for the treatment of maternal hypo-prothrombinemia and for the prevention of drug-induced hemorrhages in the newborn (I.e. anti-epileptics).

Prospective cohort studies with internal controls

- Heinonen et al (1977), CPP: vitamin k analyzed along with vitamin B12 in a total of 28 exposures in the early 16 weeks uncovered 1 newborn with congenital anomalies (ARR = 0.8; CI 95%: 0.1-5.2).

Feto-neonatal effects: This drug may cause fetal hyperbilirubinemia and kernicterus at the end of pregnancy (Finkel 1961; Wynn 1963; Lane and Hathaway 1985). Besides, it does not significantly reduce the risk of periventricular hemorrhages (Crowther and Henderson-Smart 2001).

Conclusions: There is no written evidence of an association between vitamin K and an increase in the population background reproductive risk. In case of exposure such a risk is not likely at all, due to the 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).

B02BX – More systemic hemostatic drugs

Ethamsylate – B02BX01

This is a capillary-protector and anti-hemorrhages. 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.

Carbazochrome – B02BX02

This hemostatic agent is also a capillary-protector and it is an adrenaline derivative through oxidation. It has no sympathomimetic activity and it does not affect coagulation factors, it rather affects the vasoactive component of the hemocoagulative phenomenon. Available in Italy since 1964.

Cohort studies without control

- Marchese and Moser (1966): 70 healthy newborns, some exposed in the first trimester, others in the second trimester of pregnancy.

B02BX class conclusion: There is no written evidence of specific studies concerning the use in human pregnancy of drugs in this therapeutic group. 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).

B03 – Antianemic drugs

B03A – Iron preparations

(Ferrous gluconate – ferrous phosphate – ferrous polynstirensulphonate – ferric oxide sucrose – ferripolycondrium – ferritransferrine – ferriptonate – ferric ammonium citrate – ferromaltose – ferrous gluconate sodium – ferrous maltose). Iron is an essential mineral in dietary. Demand of iron during gestation increases significantly. Iron supplement of 60-100 mg/die is therefore recommended in pregnancy, to be preferably taken not in association with multivitamin drugs, since the latter determine a decrease in the absorption (Cunningham et al 1989). Iron supplementation reduces the number of women having low Hb (<10-10.5 g/dl) but it has no clinically remarkable effect on maternal or fetal outcomes.

Conclusions: Iron supplementation is not usually necessary until 20th-28th week of gestation. Hemoglobin levels different from average in pregnancy require further tests and, if the case, iron supplementation (Royal College of Obstetrics and Gynecology 2003).

B06AA – Enzymes

Bromelain – B06AA11

This enzyme has a proteolytic direct action. It has an antiphlogistic, antiaedemigenic and fibrinolytic action. 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

Promelase – B06AA49

This is a proteolytic enzyme. 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.

Serratiopeptidase – B06AA49

It is a proteolytic enzyme derivative of Serratia. 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.

B06AA class conclusion: There is no written evidence of specific studies concerning the use in human pregnancy of drugs in this therapeutic group. 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).