

L – Antineoplastic agents and immunomodifiers

L01 – Antineoplastic agents

This is a group of heterogeneous drugs, both from chemical and pharmacological viewpoint. They are employed aiming at killing neoplastic cells as they are reproducing themselves. Their activity try to block some of the needed components to metabolism and cell reproduction or else change environmental conditions for the tumor to develop.

Some antineoplastic agents are to be exclusively used at hospital (H) and not available elsewhere. This is why we do not deal with them.

Alkylating agents (L01A)	Nitrogen mustards (L01AA)	Alkyl sulfur mustards (L01AB)	Etilenimine (L01AC)	Nitrosoureas (L01AD)	Others (L01AX)
	Cyclophosphamide	Busulfan	Tiotepa (H)	Fotemustina (H)	Pipobromano
	Chlorambucil				Temozolomide (H)
	Melfalan				Dacarbazine (H)
	Ifosfamide (H)				
Antimetabolites (L01B)	Analogs of folic acid (L01BA)	Analogs of Purine (L01BB)	Analogs of Pyrimidine (L01BC)		
	Methotrexate	Mercaptopurine	Cytarabine (H)		
	Raltitrexed (H)	Thioguanine	Fluorouracil		
		Cladribine	Tegafur		
		Fludarabine (H)	Gemcitabina (H)		
			Capecitabina (H)		
Natural Alkaloids (L01C)	Vinca Alkaloids (L01CA)	Podofiloxine derivatives (L01CB)			
	Vinblastina (H)	Etoposide			
	Vincristine	Teniposide (H)			
	Vindesina (H)	Docetaxel (H)			
	Vinorelbina (H)				
Cytotoxic antibiotics (L01D)	Actinomycins (L01DA)	Antracyclins (L01DB)	Others (L01DC)		
	Dactinomycin (H)	Doxorubicin (H)	Bleomicin (H)		
		Daunorubicin	Mitomycin (H)		
		Epirubicina (H)			
		Idarubicina			
		Mitoxantrone			
Others (L01X)	Platinum compounds (L01XA)	Metilidrazin (L01XB)	Antibodies Monoclonali (L01XC)	Others used in photodynamic therapy (L01XD)	Others (L01XX)
	Cisplatino	Procarbazina	Rituximab (H)	Verteporfina (H)	Idroxicarbamide

	Carboplatino		Trastuzumab (H)		Lonidamina
	Oxaliplatino (H)				Pentostatina (H)
					Estramustina
					Tretinoina
					Topotecan (H)
					Irinotecan (H)
					Imatinib (H)

Chemotherapeutic treatment in pregnancy should not differ from the one used in any other case. It is nonetheless prudent to delay the beginning of therapy to at least week then and, better, week 14-15. Coexistence of malignant neoplasia and pregnancy occurs in 0.07% of the cases (Sorosky et al 1997). Antimetabolites and Alkylating agents are teratogenic when administered in the first trimester. In the second and third trimester they may cause transitory neonatal myelodysplasia, pancytopenia, intrauterine reduced growth (Aviles et al 1991), low neonatal weight (Nicholson 1968, Zemlickis et al 1992), usual karyotype but chromosomal aberrations consisting of fragmentations and rings Schleuning and Clemm 1987). Complexity of different chemotherapies and possible association with radiotherapy do not often allow isolating outcomes attributable to various drugs. As far as antineoplastic agents, only case reports or small cohort studies without controls are available in literature.

Literature review

- Sweet and Kinzie (1976): literature review up to 1975, comprehending Nicholson's review (1967). 112 first trimester exposures to antineoplastic (apart from aminopterin): 9 newborns with congenital anomalies and 73 newborns with no congenital anomalies exposed after the first trimester.

Cohort studies without controls

- Mickey et al (1979): 10 first trimester exposures to chemotherapy for Hodgkin disease: 5 VIP, 1 miscarriage, 4 term births 2 of which were healthy infants and two had congenital anomalies (cleft palate and hydrocephaly). Two healthy newborns exposed after the first trimester.
- Aviles and Neri (2001), enrichment of the survey by Aviles et al (1988 and 1991): long-term follow-up (average 18.7 years, range 6-29 years) of 84 newborns born to women treated during pregnancy (38 of whom in the 1st trimester) with various chemotherapies for leukemia (29) or lymphomas (55). There was no increase in congenital anomalies and none of the newborns, including 12 of second generation (born to some exposed in uterus) showed neither neurological nor psychological disorders, or tumors.

L01A – Alkylating agents

L01AA – Analogs of Nitrogen Mustard

Cyclophosphamide – L01AA01

This is an alkylating agent inactive per se and therefore non-toxic, that is transformed by phosphorus-amidases (a high percentage of this enzyme can be found in many tumors, but it is almost absent in normal cells) into active metabolite, phosphoramidate mustard and acroleine (Mirkes 1985). Such an activity causes cyclophosphamide to select tumor cells while saving healthy cells. Patented in 1962.

Case report and cohort studies without controls

- 20 healthy newborns exposed in the first trimester of pregnancy to cyclophosphamide alone or associated to other drugs have been reported. (Marazzini and Macchi 1966, Sinkowcs and Shullenberger 1969, Coates 1970, Maher and Schreiner 1970, Lergier 1974, Symington et al 1977, Rosenschein et al 1979, Blatt et al 1980, Pizzuto et al 1980, Card 1980, Falkson 1980, Garcia et al 1981, Sosa Munoz et al 1983, Reynoso 1987, Aviles 1988 and 1991).
- Greenberg and Tanaka (1964): 1 low-weight newborn exposed from the 4th to 11th week of pregnancy to cyclophosphamide e.v. and radiotherapy for maternal Hodgkin disease, showing cleft palate, flat nasal bridge, hypoplasia of the middle phalanx of the fifth toe, bilateral absence of the big toe, abdominal cutaneous appendage and bilateral inguinal hernia.
- Coates (1970): 1 newborn exposed in the first trimester of pregnancy to cyclophosphamide for maternal nephrotic syndrome, showing hemangioma and umbilical hernia.
- Toledo et al (1971): 1 fetus (VIP) of 6 months exposed in the first trimester of pregnancy to cyclophosphamide and radiotherapy for maternal Hodgkin disease, showing total absence of toes and single coronary artery.
- Stern and Johnson (1982): 1 fetus (VIP) exposed to cyclophosphamide showing total absence of toes.
- Sosa Munoz et al (1983): 2 newborns exposed to cyclophosphamide and other antitumorals in the first trimester, one showing minor defects, the other with not specified "severe malformations", deceased.
- Murray et al (1984): 1 newborn exposed in the first trimester to cyclophosphamide, radiotherapy and doxorubicin, showing imperforate anus, rectovaginal fistula and growth retardation.
- Reynoso et al (1987): a multiple pregnancy exposed to cyclophosphamide and prednisone since the beginning of pregnancy and until 4 weeks prior to birth, that occurred at week 37. The female twin, at 17 years of age, showed a normal physical, sexual and psychological growth, while her male co-twin showed hemimelia of right upper limb and absence of thumb, esophageal atresia, alteration of vena cava, bilateral cryptorchidism, bilateral double renal ?? distretto??, mental retardation at 11 years of age, suprarenal neuroblastoma at 14 years, metastatic carcinoma of the thyroid at 16 years of age.
- Mulvihill et al (1987): 1 still birth exposed since the 6th week of gestation to mercaptopurine and since the 8th week to cyclophosphamide, showing polydactyly.
- Kirshon et al (1988): 1 newborn exposed to cyclophosphamide on day 15 and 45 of pregnancy with absence of thumbs, cleft palate, blepharophimosis, microphthalmia, hypotonia and growth retardation at 10 months of age.
- Aviles and Nitz (1988), Aviles et al (1991): 21 healthy newborns exposed to cyclophosphamide and other antineoplastic agents in pregnancy, 11 of whom in the first trimester
- Mutchinick et al (1992): 1 exposed to cyclophosphamide alone, 1,200 mg, at 5th-6th week of pregnancy for the treatment of maternal SLE, showing multiple non-specified defects.
- Zemlickis et al (1993): twin pregnancy exposed to cyclophosphamide and prednisone. The male twin had multiple congenital abnormalities at birth, and subsequently showed low IQ and developed papillary thyroid cancer at 11 years of age and neuroblastoma when aged 14, while his female co-twin was unaffected.
- Enns et al (1999): 1 newborn exposed in the first trimester to cyclophosphamide and other drugs in the treatment of maternal SLE had growth retardation, micro-brachycephaly, craniosynostosis, facial

dysmorphism (blepharophimosis, flat nasal bridge, external ear abnormalities, hypotelorism, micrognathia), hypoplasia of the thumb and absence of 4th and 5th toes of both feet. The author of this report suggests the existence of a specific syndrome pattern.

Feto-neonatal effects: no cardiotoxic neonatal effects were found in a newborn exposed in the 2nd trimester to cyclophosphamide and doxorubicin (Meyer-Wittkopf et al 2001). 66 healthy newborns have been reported in literature exposed after the first trimester to cyclophosphamide alone or in association with other antineoplastic drugs. (Lacher 1966, Krueger 1976, Sears 1976, Ortega 1977, Durodola 1979, Weed 1979, Daly 1980, Pizzuto 1980, Schartz 1981, Lowenthal 1982, Awidi 1983, Berrebi 1983, Haerr 1985, Reynoso 1987, Sigler 1988, Turchi 1988, Kim and Park 1989, Aviles et al 1991, Kim et al 1992, Theriault et al 1992, Henderson et al 1993, Luirise et al 1997, Dayoan et al 1998, Berry et al 1999, Kart et al 2001, Meyer-Wittkopf et al 2001).

Conclusions: Cyclophosphamide appears to be teratogenic, but this is confirmed only by case-reports where other antitumors are mostly used. Multiple defects, having different origin, are often detected (i.e. craniosynostosis, facies peculiare, hypoagenesias of limbs, cleft palate and eye abnormalities). Shardein (2000) has surveyed the whole of the case reports found in literature and assessed the risk of congenital anomalies around 33% in case of exposure to cyclophosphamide in the first trimester of pregnancy. Such an estimate is based only on those published cases bearing a sub-reference to healthy newborns and is to be considered as the highest figure. The use of this drug in the second and third trimester appears to show no particular risk for the fetus, although immunosuppressing effects were described.

Chlorambucil – L01AA02

This agent has been shown in vitro to block the initiation step of DNA replication. It is available in Italy since 1982.

Case report and cohort studies without controls

- 5 healthy newborns have been reported in literature exposed in the first trimester of pregnancy to chlorambucil in association with other antineoplastic agents (Baynes et al 1968, Sieber and Adamson 1975, Ba-Thike 1990, Jacobs et al 1981).
- Shotton and Monie (1963): 1 newborn exposed early in pregnancy to radiotherapy and from the 4th to 18th week to chlorambucil, showing renal agenesis and of the left ureter.
- Rugh and Skaredoff (1965): 1 fetus exposed at 3rd-4th week to chlorambucil, showing retinal defect.
- Steege and Cadwell (1980): induced abortion of 2 twins exposed to chlorambucil and prednisone at week 20 for maternal SLE. One of them had renal agenesis and of the left ureter.
- Thompson and Conklin (1983): 1 newborn exposed at 10 week of gestation to chlorambucil and steroids, deceased following severe congenital cardiopathy.

Feto-neonatal effects: 8 healthy newborns have been reported in literature exposed after the first trimester to chlorambucil in association with other antineoplastic agents (Smith 1958, Sokal and Lessmann 1960, Mangiameli 1961, Baynes 1968, Freedman 1968, Schein and Winokur 1975, Jacobs et al 1981).

Conclusions: Schardein (2000) has assessed the malformation risk at 66% in case of exposure to chlorambucil in the first trimester of pregnancy. Such an estimate is based only on those published cases bearing a sub-reference to healthy newborns and is to be considered as the highest figure.

Melfalan – L01AA03

It is available in Italy since 1969.

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

L01AA Class Conclusions: Alkylating drugs can be teratogenic if administered in the first trimester of pregnancy. In the 2nd and 3rd trimester they may be causative of transitory neonatal myelo-depression, pancytopenia and intrauterine growth retardation (Aviles et al 1991), low neonatal weight (Nicholson 1968, Zemlickis et al 1992), normal karyotype but with chromosomal abnormalities consisting of fragmentations and rings (Schleuning and Clemm 1987).

L01AB – Alkyl-sulphonates

Busulfan – L01AB01

It is available in Italy since 1955.

Case report and cohorts studies without controls

- 46 healthy newborns exposed in the first trimester and 12 healthy newborns exposed after the first trimester to busulfan alone or in association with other antineoplastic agents were reported in literature. (Izumi 1956, Sherman and Locke 1958, Coers 1959, Pest 1960, Ruiz Reyes e Tamayo-Perez 1961, White 1962, Bilski-Pasquier et al 1962, Neu 1962, Lee et al 1962, Nishimura 1964, Tennis and Stein 1965, Earll and May 1965, Williams 1966, Smalley and Wall 1966, Dugdale and Fort 1967, Frid-de Guttman 1968, Nicholson 1968, Korbitz and Reiquam 1969, Uhl et al 1969, Nolan et al 1971, Gililland et al 1983, Zuazu et al 1991, Ozumba and Obi 1992, Norhaya et al 1994).
- Diamond et al (1960): 1 newborn exposed in the first trimester to busulfan and mercaptopurine with intrauterine growth retardation, cleft palate, clouded cornea and poorly developed external genitalia, deceased on day 10 of birth
- De Rezende et al (1965): 1 abortion on week 20 exposed to busulfan and mercaptopurine showing non-specified congenital anomalies
- Nicholson (1968): 2 newborns exposed in the first trimester to busulfan and mercaptopurine. One of them had pyloric stenosis and the other an anomalous left hepatic lobe, a bilobar spleen, and pulmonary atelectasis.
- Abramovici et al (1978): 1 exposed fetus aborted at 6th week with myeloskisis
- Gililland et al (1983): 1 newborn exposed in the first trimester had intrauterine growth retardation, left hydronephrosis, hydroureter, absence of the right kidney and ureter, hepatic calcifications.
- Szentcsiki et al (1982): 1 newborn exposed in the first trimester had non-specified multiple malformations.

Feto-neonatal effects: there are no adverse outcomes on the psycho-fisical development of exposed infants (Lee et al 1962). Multiple congenital anomalies (renal agenesis, hydronephrosis and hepatic calcifications) and intrauterine growth retardation in an exposed on 20th week to busulfan and allopurinol (Boros and Reynolds 1977). Retinal degeneration in an exposed in the 3rd trimester (Saroux and Lanfrancois 1977).

Conclusions: Schardein (2000) has assessed the malformation risk at 15% in case of exposure to busulfan in the first trimester of pregnancy. Such an estimate is based only on those published cases bearing a sub-reference to healthy newborns and is to be considered as the highest figure.

L01AX – More alkylating agents

Pipobroman – L01AX02

There is no written evidence of specific studies concerning its use during human pregnancy.

Studies on laboratory animals

- Nagai (1972): teratogenic in mice and rats (30 mg/kg) for limb, tale and face malformations.

L01B – Antimetabolites

L01BA – Analogs of folic acid

Methotrexate – L01BA01

It is a methyl derivative of amipeptine. Patented in 1974.

Case report of exposures to aminopterin and methotrexate for abortive purposes.

- Thiersch (1952) (1956): 13 first trimester exposures to 6-12 mg/day of aminopterin for abortive purposes: 4 fetuses had congenital anomalies (hydrocephalous; cleft/lip palate; hydrocephalous with meningomyelocele and anencefaly).
- Meltzer (1956): 1 newborn exposed from 6th to 8th week to aminopterin for abortive purposes had craniosynostosis, bone lacunae and talipes equinovarus.
- Warkany et al (1959): 1 newborn exposed in early pregnancy to aminopterin for abortive purposes, had intrauterine growth retardation, large but soft head, due to ossification impairment, external ear abnormalities, mandibular hypoplasia, cleft palate and misplaced lower limbs.
- Goetsch (1962): aminopterin was used as abortifacient in 20 studied cases. 5 of them turned out unsuccessfully and surgical survey uncovered 1 fetus with multiple non-specified malformations.
- De Alvarez (1962): 2 newborns with hydrocephaly were exposed at the beginning of pregnancy to aminopterin with abortive purposes.
- Emerson (1962): 1 fetus of 24 weeks exposed to aminopterin to provoke abortion on week 6 and 8 of pregnancy, showed partial lack of cranial bones, hydrocephaly, cerebral hypoplasia, hypertelorism, external ear abnormalities, micrognathia, cleft palate and talipes equinovarus.
- Shaw and Steinbach (1968), Shaw (1972), Shaw and Rees (1980): 1 newborn exposed at 8 weeks of pregnancy to aminopterin with abortive purposes, showing growth retardation, impaired cranial ossification, micrognathia and low-positioned ears. At 17 years of age had regular social and mental growth.
- Milunsky et al (1968): 1 newborn exposed between 8 and 10 weeks of pregnancy to methotrexate to provoke abortion showed lack of forehead bones craniosynostosis, costal defects, hypertelorism, dextrocardia, lack of toes and mandibular hypoplasia.
- Brandner and Nussle (1969): 1 newborn exposed in 1st, 2nd, 5th and 6th months of pregnancy to high doses of aminopterin had growth retardation, poor cranial ossification, micrognathia, low-positioned ears, bulging eyes, myopia, stenosis of medullar space in long bones.
- Howard and Rudd (1977): 1 newborn exposed at 8 weeks of pregnancy to aminopterin to provoke abortion had craniosynostosis, hypertelorism, micrognathia, short limbs, various minor malformations.

- Reich et al (1978): 1 newborn exposed between 8th and 12th week of pregnancy to aminopterin, with abortive purposes, had impaired cranial ossification, hydrocephaly, hypertelorism, low-positioned ears, short nasal filter, feet syndactyly, brachydactyly of hands and hypoplasia of thumbs. 1 more newborn exposed between 6th and 8th week had cleft palate, multiple malformations, hypertelorism, low-positioned ears and regular intelligence.
- Gellis and Feingold (1979): 1 first trimester exposure to aminopterin showed reduced lower limbs, talipes equinovarus, and facial dysmorphism.
- Hill and Tennyson (1984): 1 newborn exposed prior to conception to aminopterin had intrauterine growth retardation, cranial defects, micrognathia, microphthalmia, cleft lip and clubfoot.
- Wheeler et al (2002): 1 newborn exposed in week 8 to methotrexate and misoprostol as abortifacients had multiple congenital defects and growth retardation.

Case report and cohort studies without controls

- About 800 healthy newborns have been reported in literature. Over half of them had been exposed in the first trimester to methotrexate alone or in association with other antineoplastic drugs. (Thiersch 1952, 1956, Harris 1953, Cariati 1955, Smith et al 1958, Freedman et al 1962, Goetsch 1962, Karnofsky 1967, van Thiel et al 1970, Cohen et al 1971, Pizzuto et al 1980, Blatt et al 1980, Dara et al 1981, Perry 1983, Rustin et al 1984, Hsieh et al 1985, Aviles et al 1988, Feliu et al 1988, Stovall et al 1990, Kozlowski et al 1990, Aviles et al 1991, Feldkamp e Carey 1993, Donnenfeld et al 1994).
- Powell and Ekert (1971): 1 newborn exposed from the beginning of pregnancy until week 8 to 5 mg/day (240 mg in overall) of methotrexate for the treatment of psoriasis, had craniostenosis, nasal hypoplasia, auricles and eyes defects.
- Diniz et al (1978): 1 newborn exposed from 8th to 32nd week to methotrexate, for hydatiform mole, had hydrocephaly, micrognathia, hypertelorism, auricles and cranial defects, and clitoral hypertrophy.
- Buckley et al (1997): 1 first trimester exposure to low doses of methotrexate had the classical symptoms of embriopathy from aminopterin.
- Bawle et al (1998): 1 first trimester exposure to methotrexate had craniofacial and digit defects, growth retardation and normal IQ. Another first trimester exposure to methotrexate, fluorouracil and radiations had craniofacial abnormalities, microcefaly, growth retardation and light mental retardation. 1 first trimester exposure to methotrexate had craniofacial defects and regular psychomotor development at 3 years of age.
- Del Campo et al (1999): 1 first trimester exposure had craniofacial abnormalities and mental retardation.
- Nguyen et al (2002): 1 fetus (VIP after prenatal echography) exposed to 7.5 mg/day for maternal psoriasis 2 days during the 3rd week of gestation to methotrexate had craniofacial defects, skeleton defects, cardio-pulmonary impairments and gastrointestinal anomalies. This survey suggests that methotrexate can be teratogenic also at low doses and when shortly administered.

Feto-neonatal effects: pancytopenia (Pizzuto et al 1980); transitory myelo-suppression (Okura et al 1979, Tokuda et al 1994); regular karyotype, but chromosomal aberrations consisting of fragmentations and rings (Schleuning e Clemm 1987). 68 healthy newborns exposed after the first trimester to methotrexate alone or in association with other antineoplastic drugs have been reported in literature. (Hill 1958 and 1960, Frenkel and Meyers 1960, Freedman 1962, Vecchietti and Onnis 1967, Nicholson 1968, Coopland et al 1969, Raich et al 1975, Kursid and Salem 1978, Okun et al 1979, Doney et al 1979, O'Donnell et al

1979, Blatt et al 1980, Pizzuto et al 1980, Dara et al 1981, Burnier 1981, Onnis et al 1983, Awidi et al 1983, Berrebi et al 1983, Karlap et al 1983, Aviles et al 1988, Turchi and Villasis 1988, Donnenfeld et al 1994, Giacalone et al 1999).

Conclusions: Teratogenicity of antagonists of folic acid has been well known for a long time, now. Aminopterin syndrome could be pointed out thanks to several reported fetuses and/or newborns showing congenital anomalies following exposure to aminopterin and methotrexate. The syndrome's features are craniofacial dysostosis bearing poor ossification of forehead and cranial bones, hypertelorism, micrognathia and external ear abnormalities. Cleft palate and hydrocephaly, beside other minor digit malformations can be found. Sometimes also mental retardation can be associated.

Schardein (2000) reckons that the risk for congenital anomalies is of 1.0-1.5% in case of exposure to methotrexate in the first trimester of pregnancy. The risk rate appears to be connected with the dosage, while embriopathy may occur also at 10 mg/week intake in the first trimester, especially when the drug is administered between 6 and 8 weeks (Feldkamp and Carey 1993). In case of exposure the treatment should be promptly suspended and substituted with folic acid (Lloyd et al 1999).

L01BB – Analogs of purine

Mercaptopurine – L01BB02

This is an antimetabolite. It is available in Italy since 1955.

Case report and cohort studies without controls

- 50 healthy newborns have been reported in literature exposed in the first trimester of pregnancy to mercaptopurine alone or in association with other antineoplastic agents. (Merskey and Rigal 1956, Smith et al 1958, Parekh et al 1959, Rothberg et al 1959, Frenkel and Meyers 1960, Loyd 1961, Mangiameli 1961, Lee et al 1962, Sinykin and Kaplan 1962, Bilski-Pasquier et al 1962, Raichs 1962, Revenna and Stein 1963, Shearman et al 1963, Karnofsky 1964, Moloney 1964, Hoover e Schumacher 1966, Nicholson 1968, Coopland et al 1969, Caplan et al 1970, McConnell e Bhoola 1973, Wegelius 1975, Kursid e Salem 1978, Doney et al 1979, Okun et al 1979, Blatt et al 1980, Pizzuto et al 1980, Dara et al 1981, Burnier 1981, Gililland et al 1983, Sosa Munoz et al 1983, Haerr e Pratt 1985, Turchi and Villasis 1988, Feliu et al 1988, Aviles et al 1991, Zuazu et al 1991, Azuno et al 1995).
- Diamond et al (1960): 1 newborn exposed in the first trimester to busulfan and mercaptopurine had reduced intrauterine growth, cleft palate, clouded cornea and microphthalmia, low development of external genitalia. He died at 10 days of age.
- Mulvihill et al (1987): 1 still birth exposed on week 6 of gestation to mercaptopurine and since 8th week to cyclophosphamide had polydactyly.

Retrospective cohort studies with internal controls

- Francella et al (2003): of 271 pregnancies of women suffering from intestinal inflammatory disease, 39 were exposed to mercaptopurine (24 in the first trimester and 15 throughout pregnancy). 132 non-exposed controls. The incidence of miscarriages was of 13% in the exposures vs. 28% in the control group. One newborn with congenital anomaly (hydrocephaly) among exposed (1/132) vs. 4 newborns with congenital anomalies among the controls (4/94).

Feto-neonatal effects: pancytopenia (Pizzuto et al 1980); transitory myelosuppression (Okun et al 1979); hemolytic anemia (McConnell and Bhoola 1973); regular psychophysics development and cytogenetic analysis in 6 exposures with a follow-up for 3-19 years (Aviles et al 1991); normal karyotype, but

chromosomal aberrations consisting in fragmentations and rings (Schleuning and Clemm 1987). 48 healthy newborns have been reported in literature exposed after the first trimester to mercaptopurine alone or in association with other neoplastic agents (Frenkel and Meyers 1960, Loyd 1961, Lee et al 1962, Moloney 1964, Nicholson 1968, Coopland et al 1969, McConnell and Bhoola 1973, Kursid and Salem 1978, Doney et al 1979, Okun et al 1979, Pizzuto et al 1980, Dara et al 1981, Burnier 1981, Gililand et al 1983, Haerr and Pratt 1985, Turchi and Villasis 1988, Feliu et al 1988, Aviles et al 1991, Azuno et al 1995).

Conclusions: the risk of malformation is assessed as 1:25 in case of exposure to mercaptopurine in the first trimester of pregnancy. Such an assessment derives only from published cases where a sub-reference of live births is mentioned and it is to be considered as the highest feature.

Thioguanine – L01BB03

This is an antimetabolite, analog of purines. It is available in Italy since 1974.

Case report

- Maurer et al (1971): 1 fetus (VIP) of 24 weeks exposed to cytarabine and thioguanine on week 20 of pregnancy had trisomy C. A second pregnancy exposed to the same type of chemotherapy has not shown congenital anomalies of the fetus therapeutically aborted.
- Schafer (1981): 1 newborn exposed throughout pregnancy to cytarabine and thioguanine showed absence of the 3rd toes and of distal phalanx of thumbs. A subsequent pregnancy exposed to the same treatment turned out a healthy newborn. Another healthy newborn had been exposed in the first trimester of pregnancy to thioguanine in association with other neoplastic agents.
- Artlich et al (1994): 1 newborn exposed on 6 week of pregnancy to cytarabine, daunorubicin, doxorubicin and thioguanine had brachicephaly, and cranial and skeleton defects.

Feto-neonatal effects: 25 healthy newborns exposed after the 1st trimester to thioguanine alone or in association with other antineoplastic agents have been reported in literature (Pawlinger et al 1971, Auyong et al 1972, Raich and Curet 1975, Gokal et al 1976, Moreno et al 1977, Doney 1979, Hamer 1979, Manoharan and Leydan 1979, O'Donnell et al 1979, Taylor and Blom 1980, Tobias and Bloom 1980, Plows 1982, De Souza et al 1982, Lowenthal et al 1982, Awidi et al 1983, Catanzarite and Ferguson 1984, Volkenandt et al 1987, Reinoso et al 1987, Feliu et al 1988, D'Emilio et al 1989, Veneri et al 1996).

Conclusions: We have not been able to find specific studies concerning the use of this drug in human pregnancy. The drug is potentially teratogenic.

Cladribine – L01BB04

There are no specific studies in literature concerning its use in human pregnancy.

Studies on laboratory animals

- Shalko et al (1995): teratogenic in rabbits (3 mg/kg), no adverse effects in mice (0.5 mg/kg) and rabbits (1 mg/kg).
- Mitala et al (1996): microphthalmia in mice.
- Lau et al (2001): microphthalmia in rats.

L01BC – Analogs of Pyrimidin

Fluorouracil – L01BC02

It interferes with the synthesis of DNA and RNA. 6% of it is absorbed via cutis, but its absorption via mucosa is unknown. It is available in Italy since 1965.

Case report

- Stephens et al (1980) 1 fetus (VIP) of 16 weeks exposed since week 11-12 and for a month to fluorouracil, tetracycline and 5rad had bilateral aplasia of radius and digit anomalies, pulmonary hypoplasia, of the aorta, of thymus and of ductus bilifer, esophageal aplasia of duodenum and of ureter, imperforate anus, single umbilical vein, renal dysplasia and common rectum and bladder.
- Odom et al (1990): 2 healthy newborns exposed in the first trimester to topic fluorouracil in vagina and 5 healthy newborns exposed in the first trimester via cutis.
- Otano et al (1992): 5 exposures per vaginal way to fluoruracil turned out 4 healthy newborns and one Down' Syndrome.
- Zemlickis et al (1992): 2 exposures in the first trimester to fluorouracil combined with other antineoplastic agents. One miscarriage and 1 healthy newborn

Retrospective cohort studies with internal controls

- Rosa (1993), Michigan MSS: of 14 first trimester exposures also via other than systemic ways, 1 newborn had major defects, one expected. RR = 1.1 (CI 95%: 0.5-5.6).

Feto-neonatal effects: reversible toxicity from fluorouracil in an infant exposed in the 4th and 6th month of pregnancy (Stadler and Knowles 1971), anemia (Cuvier et al 1997), reduced intrauterin growth (Dreicer and Love 1991, Zemlickis et al 1992). 49 newborns exposed after the first trimester of pregnancy to fluorouracil, in association with other neoplastic agents have been reported in literature. (Stadler and Knowles 1971, Turchi et al 1988, Dreicer and Love 1991, Theriault et al 1992, Zemlickis et al 1992, Cuvier et al 1997, Giacalone et al 1999 and Berry et al 1999).

Conclusions: We have not been able to find any specific study concerning the use of this drug in human pregnancy, but few records of exposed cases. This drug is not likely teratogenic.

Tegafur – L01BC03

This drug is available in Italy since 2000.

No specific studies are available in literature relevant to its use in human pregnancy.

Studies on laboratory animals

- Furuhashi et al (1966): nonteratogenic in rats at doses up to 7 mg/kg/day per os.
- Yukiyaama et al (1966): nonteratogenic in rats at doses up to 5 mg/kg/day per os. Hydrocephaly and visceral anomalies appear to increase at doses as high as 7 mg/kg/day per os.
- Shinomiya et al (1966): nonteratogenic in rats at doses up to 4 mg/kg/day per os. Slow fetal ossification at doses as high as 7 mg/kg/day per os
- Shinomiya et al (1966): nonteratogenic in rabbits at doses up to 1.5 mg/kg/day per os. Fetal mortality, reduced fetal growth and teratogenicity at doses as high as 2-6 mg/kg/day per os.

Conclusions: No specific studies are available in literature relevant to its use in human pregnancy. The sole possible assessment is based on studies on laboratory animals, that have showed teratogenicity of the drug.

L01C – Alkaloids derived from plants and other natural products

L01CA – Vinca alkaloids and their analogs

Vincristine – L01CA02

This is an antimitotic, vinca alkaloid. It is available in Italy since 1967.

Case report and cohort studies without controls

- 40 healthy newborns exposed in the first trimester to vincristine alone or in association with other antineoplastic agents have been reported in literature. (Armstrong et al 1964, Rosenzweig et al 1964, Chassagne et al 1965, Shein and Winokun 1975, Sears and Reid 1976, Thomas and Pecknam 1976, McKeen et al 1979, Blatt et al 1980, Falkson et al 1980, Pizzuto et al 1980, Garcia et al 1981, Feliu et al 1988, Aviles et al 1988 e 1991, Zemlickis et al 1992).
- Mennuti et al (1975): 1 fetus (VIP) exposed in the 1st trimester of pregnancy to vincristine, procarbazine, mechlorethamine and steroids, had renal hypoplasia.
- Thomas and Pecknam (1976): 1 newborn exposed in the 1st trimester of pregnancy to vinblastine, vincristine and procarbazine had a minor atrial septal defect "tipo secundum". Deceased after severe respiratory distress syndrome.
- Mulvihill et al (1987): 1 newborn exposed since conception to vincristine, lomustine, procarbazine and prednisone had cleft lip/palate.
- Mc Keen et al (1979): 2 newborns exposed in the 1st trimester of pregnancy to MOPP (Mechlorethamine, Vincristine, Procarbazine and Prednisone), showing hydrocephaly and cleft lip/palate respectively.
- Zemlickis et al (1992): 1 newborn exposed in the 1st trimester of pregnancy to vincristine and other antineoplastic agents, had hydrocephaly.

Feto-neonatal effects: pancytopenia (Pizzuto et al 1980); transitory myelosuppression (Okun et al 1979); regular karyotype with chromosomal aberrations (fragmentations and rings) exposed also to other antineoplastic agents (Schleuning and Clemm 1987). 75 healthy newborns exposed after the 1st trimester to vincristine alone or in association with other antineoplastic agents have been reported in literature. (Lacher and Yeller 1966, Coopland et al 1969, Pawlinger et al 1971, Weinrach 1972, Raich et al 1975, Lilleyman et al 1976, Ho et al 1976, Ortega 1977, Durie and Giles 1977, Kursid and Salem 1978, Newcomb et al 1978, Okun et al 1979, Doney et al 1979, O'Donnell et al 1979, Jones et al 1979, McKeen et al 1979, Weed et al 1979, Blatt et al 1980, Daly et al 1980, Pizzuto et al 1980, Tobias and Bloom 1980, Colbert 1980, Dara et al 1981, Parvez et al 1981, Burnier 1982, Lowenthal et al 1982, Awidi et al 1983, Berrebi et al 1983, Gilliland and Weinstein 1983, Karp et al 1983, Fassas et al 1984, Haerr and Pratt 1985, Pektasides et al 1987, Volkenand et al 1987, Reynoso et al 1987, Sigler et al 1988, Schneider et al 1988, Turchi and Villasis 1988, Feliu et al 1988, Kim and Park 1989, Aviles et al 1988 e 1991, Sandvei et al 1990, Kim et al 1992, Giacalone et al 1999).

Conclusions: Vincristine is teratogenic. Schardein (2000) has assessed the malformation risk at 10% in case of exposure to this drug in the first trimester of pregnancy. Such an estimate is based only on those published cases bearing a sub-reference to healthy newborns and is to be considered as the highest figure.

L01CB – Podophyllotoxin derivatives

Etoposide – L01CB01

This drug is available in Italy since 2000.

We have been unable to locate references on possible human reproductive effects of this agent during the first trimester of pregnancy.

Studies on laboratory animals

- Sieber et al (1978): teratogenic in mice (0.5-1 mg/kg) mainly for esencephaly, dextrocardia and skeleton abnormalities.

Feto-neonatal effects: myelodepression (Murray 1994), leukopenia, neutropenia, deafness and alopecia (Raffles et al 1989), trombocytopenia (Hsu et al 1995), cerebral atrophy (Elit et al 1999). 17 healthy newborns exposed after the first trimester of pregnancy to etoposide alone or in association with other antineoplastic agents have been reported in literature. (Choo et al 1985, Aviles et al 1991, Buller et al 1992, Brunet et al 1993, Arango et al 1994, Horbelt et al 1994, Murray 1994, Morishita et al 1994, Hsu et al 1995, Requena et al 1995, Rodriguez and Haggag 1995, Bozeman et al 1995, Shimizu et al 2003).

Conclusions: No specific studies are available in literature on its use in human pregnancy. This drug is likely to be teratogenic.

L01BD – Anthracycline antibiotics and related agents

Daunorubicin – L01DB02

Case report and cohort studies without controls

- 9 healthy newborns exposed in the 1st trimester of pregnancy to daunorubicin in association with other antineoplastic drugs have been reported in literature. (Sears et al 1976, Garcia 1981, Alegre et al 1982, Aviles et al 1988, Feliu et al 1988, Zuazu et al 1991).
- Artlich et al (1994): 1 newborn exposed at 6 weeks of pregnancy to cytarabin, daunorubicin, doxorubicin and thioguanine, had brachycephaly, skeleton and cranial defects.

Feto-neonatal effects: 30 healthy newborns exposed after the 1st trimester to danorubicin in association with other antineoplastic agents have been reported in literature .(Gocal et al 1976, Lilleyman et al 1977, Lowenthal et al 1978, Kursid and Salem 1978, Newcomb et al 1978, Hamer et al 1979, Okun et al 1979, Doney et al 1979, O'Donnell et al 1979, Colbert et al 1980, Pizzuto et al 1980, Tobias and Bloom 1980, Dara et al 1981, Berrebi et al 1983, Cantini and Yanes 1984, Catanzarite and Ferguson 1984, Fassas et al 1984, Awidi et al 1983, Volkenandt et al 1987, Reinoso et al 1987, Sigler et al 1988, Feliu et al 1988, Aviles et al 1988, Turchi and Villasis 1988). Transitory myelodepression (Okun et al 1979, Colbert et al 1980). Regular karyotype but with chromosomal aberrations consisting of fragmentations and rings (Schleuning e Clemm 1987).

Idarubicine – L01DB06

This analog of daunorubicin is available in Italy since 1995.

We have been unable to locate references on possible human reproductive effects of this agent during the first trimester of pregnancy.

Case reports

- Siu et al (2002): 1 newborn exposed on 13th week of pregnancy to idarubicine and tretinoin had atrial septal defect.

Studies on laboratory animals

- Yamashita et al (1992): teratogenic in rats (0.2 mg/kg) for ossification retardation and still birth.
- Ono et al (1992): teratogenic in rats (0.2 mg/kg) for skeleton defects.

Feto-neonatal effects: prematurity and intrauterin reduced growth (Claahsen et al 1998); prematurity, respiratory distress, neonatal necrotizin enterocolitis, ventricular hemorrhage and cardiotoxicity (Achtari and Honfeld 2000); fetal death in an exposed also to cytarabine and mitoxantrone (Reynoso et al 1994); cardiotoxicity (Breccia et al 2002). Two healthy neaborns exposed after the 1st trimester of pregnancy to idarubicine alone or in association with other antineoplastic agents have been reported in literature (Claahsen et al 1998, Actari and Hohfeld 2000).

Conclusions: There are no specific studies relevant to its use in human pregnancy. The drug is potentially teratogenic.

Mitoxantrone – L01DB07

It is structurally related to doxorubicin. It is available in Italy since 1987.

We have been unable to locate references on possible human reproductive effects of this agent during the first trimester of pregnancy.

Studies on laboratory animals

- James et al (1983): nonteratogenic in rats (0.21 mg/kg), but increased fetal re-absorption has been noticed. It is not teratogenic in rabbits (0.5 mg/kg).

Feto-neonatal effects: fetal death in one exposure also to idarubicine and cytarabine (Reynoso et al 1994). Three healthy newborns exposed after the 1st trimester of pregnancy to mitoxantrone alone or in association with other antineoplastic agents have been reported in literature (Azuno et al 1995, Giacalone et al 1999).

Conclusions: No specific studies have been found in literature relevant to its use in human pregnancy. This drug is potentially teratogenic.

L01X – More antineoplastic agents

L01XA – Platinum compounds.

Cisplatin – L01XA01

It is a cytostatic agent available in Italy since 1997.

We have been unable to locate references on possible human reproductive effects of this agent during the first trimester of pregnancy.

Case reports

- Jacobs (1980): 1 fetus (hysterectomy) exposed to a single dose on 12th week of pregnancy did not show evident congenital defects.

Studies on laboratory animals

- Nagaoka et al (1981): nonteratogenic, although embryoethal in rats (0.54 mg/kg e.v.), but not in rabbits (0.3 mg/kg e.v.).
- Anakubi et al (1982): nonteratogenic, although embryoethal in rats and rabbits at doses up to 0.5 mg/kg intraperitoneal.
- Kopf-Maier et al (1985): nonteratogenic in mice, but causative of ossification retardation (10 mg/kg intraperitoneal).

Feto-neonatal effects: neutropenia, alopecia and deafness (Raffles et al 1989). Twelve healthy newborns exposed after the 1st trimester of pregnancy to cisplatin alone or in association with other antineoplastic agents have been reported in literature. (Chung e Birnbaum 1963, Jubb 1963, Creasman et al 1971, Bakri and Given 1984, Curtin and Adcock 1986, Malone et al 1986, Dgani et al 1989,

Christman et al 1990, Malfetano e Goldkrand 1990, King et al 1991, Buller et al 1992, Henderson et al 1993, Bayhan et al 1999, Giacalone et al 1999, Shimizu et al 2003).

Conclusions: There are no specific studies in literature relevant to its use in human pregnancy. This drug is potentially teratogenic.

Carboplatin – L01XA02

We have been unable to locate references on possible human reproductive effects of this agent during the first trimester of pregnancy.

Studies on laboratory animals

- Kai et al (1988): nonteratogenic in rats (4 mg/kg e.v.)

Feto-neonatal effects: Five healthy newborns exposed after the 1st trimester of pregnancy to carboplatin alone or in association with other antineoplastic agents have been reported in literature (Henderson et al 1993, Bozeman et al 1995, Giacalone et al 1999, Mendez et al 2003, Shimizu et al 2003).

Conclusions: There are no specific studies in literature relevant to its use in human pregnancy. This drug is potentially teratogenic.

L01XB – Methylhydrazine

Procarbazine – L01XB01

It is available in Italy since 1967.

Case report and cohort studies without controls

- Nine healthy newborns exposed in the 1st trimester of pregnancy to Procarbazine alone or in association with other neoplastic agents (Wells et al 1968, Shapira and Cludley 1984 and Aviles et al 1991).
- Wells et al (1968): 1 newborn exposed in the 1st trimester with multiple angiomas.
- Garret (1974): 1 miscarriage exposed at the beginning of the 2nd trimester of pregnancy to a MOPP (Mechlorethamine, Vinblastine, Procarbazine and Prednisone) with feet actrodactyly, syndactyly of a foot, ear defects and cerebral hemorrhage.
- Mennuti et al (1975): 1 fetus (VIP) exposed in the 1st trimester of pregnancy to vincristine, procarbazine, mechlorethamine and steroids had hypoplastic kidney
- Thomas and Pecknam (1976): 1 newborn exposed in the 1st trimester of pregnancy to vinblastine, vincristine and procarbazine had a minor atrial septal defect "tipo secundum".
- Mc Keen et al (1979): 2 newborns exposed in the 1st trimester of pregnancy to MOPP (Mechlorethamine, Vinblastine, Procarbazine and Prednisone) had hydrocephaly and cleft palate, respectively.
- Mulvihill et al (1987): 1 newborn exposed since conception to vincristine, lomustine, procarbazine and prednisone had cleft palate.
- Zemlickis et al (1992): 1 newborn exposed in the 1st trimester of pregnancy to procarbazine and other antineoplastic agents had hydrocephaly.

Feto-neonatal effects: 38 healthy newborns exposed after the 1st trimester of pregnancy to procarbazine alone have been reported in literature (Daw 1970) or in association with other antineoplastic agents (Shein and Winokur 1975, Chaube and Swinyard 1975, Thomas and Pecknam 1976, Jones and Weinerman 1979, Mc Keen et al 1979, Blatt et al 1980, Daly et al 1980 and Aviles et al 1991).

Conclusions: There are no specific studies in literature relevant to its use in human pregnancy. Only case reports are available. The use of this drug in association with other neoplastic agents makes it impossible to definitively assess its risk. The drug is potentially teratogenic.

L01XX – More antineoplastic agents

Hydroxycarbamide (Hydroxyurea) – L01XX05

This is an inhibitor of DNA synthesis. Patented in 1955.

Case reports and cohort studies without controls

- Nine newborns have been reported in literature exposed in the 1st trimester of pregnancy to hydroxycarbamide alone or in association with other antineoplastic agents. (Patel et al 1991, Tertian et al 1992, Delmer et al 1992 (still birth), Jackson et al 1993, Szanto and Kovacs 1994, Cinkotai et al 1994, Charache et al 1995, Diav-Citrin et al 1999, Byrd et al 1999) and 6 healthy newborns exposed after the first trimester (Doney et al 1979, Pizzuto et al 1980, Fitzgerald e McCann 1993, Dell'Isola et al 1999).

Feto-neonatal effects: one preterm (31 weeks) healthy infant with cushingoid aspect had been exposed on 27th week to hydroxyurea in association with other antineoplastic agents and cortisone (Doney et al 1979).

Conclusions: There are no specific studies in literature relevant to its use in human pregnancy. Only case reports are available. The use of this drug in association with other neoplastic agents makes it impossible to definitively assess its risk. The drug is potentially teratogenic.

Lonidamine – L01XX07

This drug inhibits energetic mechanisms of neoplastic cells. It is available in Italy since 1997.

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

Conclusions: There are no specific studies in literature relevant to its use in human pregnancy. This drug is potentially teratogenic.

Tretinoin – L01XX14

This is a retinoid. It is available in Italy since 1988.

Case reports

- Simone et al (1995): 1 healthy newborn exposed to systemic tretinoin in the first trimester.
- Siu et al (2002): 1 newborn exposed on 13th week of pregnancy to hydroxyurea and tretinoin had atrial septal defect.

Studies on laboratory animals

- It causes malformations to the ear, eye, face, palate, limbs, neural tube and heart in monkeys, rabbits, mice, rats and guinea-pigs at doses varying between 1.5 and 7 times the human therapeutic dose (Kochhar-Christian 1977, Cohen 1993 and Nau et al 1994).

Feto-neonatal effects: fetal arrhythmia (Terada et al 1997). 23 healthy newborns have been reported in literature exposed after the 1st trimester of pregnancy to tretinoin alone or in association with other antineoplastic agents. (Caligiuri and Mayer 1989, Harrison et al 1994, Celo et al 1994, Tsuda et al 1994, Stentoft et al

1994, Hoffman et al 1995, Watanabe et al 1995, Lipovsky et al 1996, Maeda et al 1997, Incerpi et al 1997, Terada et al 1997, Delgado-Lamas and Garces-Ruiz 2000, Giangounidis et al 2000, Fadilah et al 2001, Breccia et al 2002, Carradice et al 2002 and Itoh et al 2003).

Conclusions: No specific studies are available in literature relevant to the systemic use of this drug in human pregnancy, apart from a couple of clinic reports. This agent should anyway be considered teratogenic, being a retinoid (see isotretinoin). For its topic use see D10AD01.

L01 Class conclusions: In general, although antineoplastic drugs are likely to have a high teratogenic effect on experimental animals, human fetus appears to be less liable to their activity. Congenital anomalies are particularly associated to first trimester exposures to antifolic agents. One out of six women treated with one single antineoplastic agent in the first trimester have malformed offspring, 1 out of 3 have miscarriages, the rest of them instead deliver healthy infants. It is much more difficult to make an assessment when the woman is treated to multiple chemotherapeutic agents possibly in association with radiotherapy. Teratogenic risk for exposure to antineoplastic agents is generally considered 10% higher than usual (Burniere 1982). Only 4% of women treated with a single antineoplastic agent after the 1st trimester delivers a child with congenital anomalies (Stern and Johnson 1982). 40% of in utero exposures to antineoplastic agents show reduced intrauterine growth (Nicholson 1968).

L02 – Endocrin Therapy
L02A – Hormones and related drugs
L02AB – Progestogens

Megestrol – L02AB01

This drug acts both as a progestin and anti-estrogen agent, it competes with the receptor for progesterone, androgens and glucocorticoids.

See Medroxyprogesterone G03DA02 and other progestogens.

L02AE – Analogs of gonadotropin-releasing hormone

Analogs of Gonadotropin Releasing Hormone (GnRHa) are employed to cause suppression and production of gonadotropins and they are mainly recommended to women for the treatment of endometriosis, infertility and uterine leiomyoma, and to induce ovulation during in vitro fertilization.

Literature review

- Chardonnnes et al (1998): 346 exposures to GnRHa (Martinez et al 1988, Serafini et al 1988, Dicker et al 1989, Forman et al 1990, Isherwood et al 1990, Lejeune et al 1990, Golan et al 1990, Ghazi et al 1991, Smitz et al 1991, Lockwood et al 1992, Jackson et al 1992, Herman et al 1992, Balasch et al 1993, Gonen et al 1993, Har-Toov et al 1993, Young et al 1993, Weissman and Shoham 1993, Wilshire et al 1993, Calhill et al 1994, Abu-Heija et al 1995, Chang et al 1995, Elefant et al 1995, Gartner et al 1997, and Chardonnens et al 1998). 55 miscarriages (15.9%), 24 healthy newborns exposed in the second trimester, 284 healthy newborns exposed at the beginning of pregnancy, 5 newborns showed congenital anomalies.

Cohort studies with internal controls

- Lahat et al (1999): 6 exposures to GnRHa and 20 controls. Follow-up until 7.8+/-2.0 years of age, One exposed newborn had cleft palate and 4 had neurobehavioral anomalies (1 had epilepsy, 3 hyperactivity, 3 motor difficulties and 1 language difficulties). One single infant among controls showed hyperactivity.

Buserelin – L02AE01

This hypothalamic polypeptide is a synthetic analog of gonadorelin (GnRH). It is antagonist of LH-RH receptors, and causes the elimination of LH and FSH. When the drug is administered at low doses it helps secretion of gonadotropins and gonadal steroids. At, long-term- administered high doses instead, buserelin inhibits pituitary and gonadal activity, thus determining the reduction of plasma estrogens and progesterone concentration in female subjects and it also inhibits follicular maturation. Besides, it inhibits spermatogenesis in a reversible way. It is used as contraceptive, in the treatment of endometriosis and in the treatment of steroidal-sensible neoplasias. It is available in Italy since 1985.

Literature review

- Chardonnnes et al (1998): 220 healthy newborns exposed at the beginning of pregnancy to buserelin (Martinez et al 1988, Dicker et al 1989, Forman et al 1990, Isherwood et al 1990, Lejeune et al 1990, Smitz et al 1991, Lockwood et al 1992, Jackson et al 1992, Balasch et al 1993, Gonen et al 1993, Calhill et al 1994, and Abu-Heija et al 1995), 5 newborns with congenital anomalies: cleft palate (Ron El et al 1990), bilateral clubfoot (Jackson et al 1992), hypospadias (Calhill et al 1994), persistent ductus arteriosus and another non-specified defect (Abu-Heija et al 1995).

Leuprorelin – L02AE02

85/100% of a depot dose of this drug administered i.m. is absorbed in 4 weeks. Leuporelin is employed in the treatment of endometriosis, leiomioma, and in procedures for in vitro fertilization. It is available in Italy since 1996.

Literature review

- Chardonnnes et al (1998): 21 healthy newborn exposed at the beginning of pregnancy to leuporelin (Ghazi et al 1991, Wilshire et al 1993, Young et al 1993, Chang et al 1995 and Gartner et al 1997).

Case report

- Serafini et al (1998): 1 ectopic pregnancy and 1 miscarriage occurred in exposures from day 24 to 48 and 24 to 38 after last menstruation, respectively.
- Taskin et al (1999): 4 healthy newborns exposed in early pregnancy.
- Platteau et al (2000): 2 exposed newborns had congenital anomalies (bilateral inguinal hernia and renal atresia).

Goserelin – L02AE03

This anti-androgen is synthetic analog agonist of LH-RH, pituitary-hypothalamus hormone (Gn Rha). Its long-term administration inhibits LH and FSH secretion from pituitary gland, with consequent reduction of testosterone in men and estradiol in women. It is available in Italy since 1987.

Case report

- Rocco (1992): a pair of healthy twins exposed to a depot preparation on weeks 5, 9 and 13.
- Har-Toov et al (1993): 1 healthy newborn exposed in the first month of pregnancy to a depot preparation.

Cohort studies without controls

- Wilshire et al (1993): 18 exposures in early pregnancy turned out 5 miscarriages (28%) and 13 healthy newborns.

Triptorelin – L02AE04

This is an inhibitor of pituitary-gonadotrope secretion and synthetic analog decapeptide of LH-RH. It is available in Italy since 1990.

Literature review

- Chardonnnes et al (1998): 38 healthy newborns exposed in the early weeks of gestation to triptorelin (Golan et al 1990, Herman et al 1992, Har-Toov et al 1993, Weissman and Shoham 1993, Elefant et al 1995 and Chardonnnes et al 1998).

L02AE Class Conclusions: We have only limited studies concerning the use of Gonadotropin Releasing Hormone (GnRH_a) analogs in the first trimester of pregnancy and they do not suggest an increased reproductive risk. In fact, the lack of reported anomalies in the long period of commercialization and the absence of teratogenic activity on laboratory animals is to be considered (records provided by manufacturer for registration, not available in databases).

L02B – Hormone Antagonists and related compounds

L02BA – Antiestrogens

Tamoxifen – L02BA01

This is a non-steroid antiestrogen, also used as ovulation inductor (Ruiz-Velasco 1979). Its half-life is of 7 days, it is metabolized by the liver and it creates

active metabolites having a half-life as long as up to 8 weeks. It determines premenopause in women, increases the level of circulating estrogens (up to 6 times basic values) and of progesterone, and it slightly decreases FSH, LH, PRL. It is available in Italy since 1989.

Case reports

- Tewari et al (1997): 1 female newborn exposed in the early 20 weeks of pregnancy had ambiguous genitals
- Koizumi et Aono (1986), Lai et al (1994): 3 healthy newborns exposed from prior to conception until the moment of diagnosis in pregnancy.
- Isaacs et al (2001): 1 healthy newborn exposed throughout pregnancy.

Cohort studies without controls

- Ruiz-Velasco et al (1979): 9 healthy newborns to mothers treated with tamoxifen; 5 miscarriages in exposures to tamoxifen after conception
- Cullins et al (1994), manufacturer: 37 exposures were recorded. 8 VIP, 19 healthy newborns, 10 infants/fetuses with congenital anomalies (2 of which had craniofacial defects, 1 had microtia and microsomy of half face, another had Goldenhar syndrome).

Conclusions: We have been able to find only few specific studies concerning the use of tamoxifen in human pregnancy. Nevertheless, its chemical-pharmacological analogy with diethylstilbestrol can suggest that this drug may have a similar effect on the development of genitalia. The drug has not shown teratogenic effects on laboratory animals (rats, rabbits), but it is carcinogenic in rodents (records provided by manufacturers for registration, not available in databases).

L02BG – Enzyme inhibitors

Aminoglutethimide – L02BG01

Adrenocortical suppressor, it blocks the production of cortisol and aldosterone and it is used in the treatment of Cushing syndrome. This drug decreases cholesterol conversion to pregnenolone and it determines a partial blockage of 21- and 11-hydroxylase in aromatization of androgens and estrogens. Due to its virilizing effects it is no longer marketed in the USA. It is available in Italy since 1984.

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

Case reports

- Iffy et al (1965), Marek and Horky (1970), German et al (1970), and Le Maire et al (1972): 4 female infants born with virilization signs, exposed in the 2nd and 3rd trimester of pregnancy.

Studies on laboratory animals

- Goldman (1970): virilization of external female genitalia, feminization of external male genitalia, growth retardation and increased fetal mortality was observed in rats exposed to doses 5-15 times higher than human therapeutic doses.

Conclusions: Despite the very few reports relevant to the use of aminoglutethimide in pregnancy, its chemical features suggest that its use after the first trimester of pregnancy may determine virilizing effects on female fetuses.

L03 – Immunostimulants

L03A – Cytokinins and Immunomodulators

L03AA – Colony stimulating factors

Filgrastim – L03AA02

This is a granulocyte colony-stimulating factor (G-CSF), mainly neutrophils. A glycoprotein produced from *Escherichia coli*. It is available in Italy since 1998.

Case reports

- Cavallaro et al (2000): 1 healthy newborn exposed in the first trimester
- Welte and Boxer (1997): 4 healthy newborns exposed in the 1st and 2nd trimester, 1 newborn with bilateral hydronephrosis

Feto-eonatal effects: 3 healthy newborns were exposed on weeks 24 and 26 of pregnancy to filgrastim and antiproliferative treatment (Arango et al 1994, Cavenagh et al 1995, and Sangalli et al 2001); cyclic neutropenia (Welte and Boxer 1997).

Molgramostim – L03AA03

This is a stimulating factor of macrophage and granulocyte colonies (G-CSF), a glycoprotein produced from *Escherichia coli*. It is available in Italy since 1994.

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

Lenograstim – L03AA10

This is a stimulating factor of granulocyte colonies (G-CSF), a re-combining glycoprotein. It is available in Italy since 1994.

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

L03AA Class Conclusions: There is no written evidence of specific studies concerning the use of drugs in this therapeutic class during human pregnancy. In case of exposure, the sole available information is the absence of teratogenic activity on laboratory animals (records provided by manufacturer for registration, not available in databases).

L03AB – Interferons

Interferon alfa-natural– L03AB01

Interferon beta-natural – L03AB02

Interferon gamma – L03AB03

Interferon alfa-2a – L03AB04

Interferon alfa-2b– L03AB05

Interferon alfa-n1 – L03AB06

Interferon beta-1a – L03AB07

Interferon beta-1b – L03AB08

Interferon alfacon-1 – L03AB09

Peginterferon alfa-2b – L03AB10

Glycoprotein produced by normal human cells responding to viral infections, able to interfere with the metabolism of non-infected cells to create a status of antiviral resistance. Its production is based on the induction of cell culture, extraction of raw protein fraction and its purification by means of affinity chromatography. Beside the activity of inducer of antiviral resistance, it appears to have cyto-modifying, cyto-

inhibiting and immuno-modulating capacity. Interferone alfa has a molecular weight of 19,000 Dalton and only a very low percentage crosses the placenta. The first interferone was available in Italy in 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.

Case reports

- Crump et al (1992), Baer et al (1992), Delmer et al (1992), Reichel et al (1992), Petit et al (1992), Pardini et al (1993), Williams et al (1994), Sakata (1995), Lipton et al (1996), Ruggiero et al (1996), Pulik et al (1996), Shpilberg et al (1996), Iki et al (1999), Trotter eandZygmunt (2001), and Mubarak et al (2002): 17 healthy newborns exposed to interfeon alfa in the 1st trimester of pregnancy.

Studies on laboratory animals

- Naya et al (1988): nonteratogenic in rats at doses 310 times the human doses of interferon beta.
- Ohnishi et al (1992): nonteratogenic in rats and rabbits at doses up to 1 mg/kg e.v. of interferon gamma.

Feto-neonatal effects: there were no adverse outcomes in exposures after the 1st trimester. (Maria 1991, Baer et al 1992, Maria 1992, Reichel et al 1992, Jose and Manuel 1992, Perez-Encins et al 1994, Thornley e Manoharan 1994, Vianelli et al 1994, Sakata 1995, Delage et al 1996, Huggston and Adransson 1996, Lipton et al 1996, Milano et al 1996, Ruggiero et al 1996, Kuroiwa et al 1998, Mancuso et al 1998, Iki et al 1999, Hiratsuka et al 2000, Echols et al 2001, Baykal et al 2002, and Ozaslan et al 2002); transitory neonatal thrombocytopenia (Mubarak et al 2002).

L03AB Class Conclusions: There is no written evidence of specific studies concerning the use of interferons in the first trimester of human pregnancy. Only exposed healthy newborns have been reported. In case of exposure the following should be noticed: absence of congenital defects in clinic records and absence of teratogenic activity in laboratory animals (records were also provided by manufacturer for registration).

L03AX – More cytokynes and immunomodulators

Pidotimod – L03AX05

This immunostimulating agent induces maturation of linfocytes T and stimulates macrophages. 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.

Timopentina – L03AX09

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.

L03AX Class Conclusions: There is no written evidence of specific studies concerning the use of interferons in human pregnancy. The sole possible evaluation is based on laboratory animals studies that have not revealed any teratogenic activity of drugs in this therapeutic class (records provided by manufacturer for registration, not available in databases).

L04 – Immunosuppressant drugs

Immunosuppressant therapy recommends organ transplantation, newborn prevention of hemolytic disease from Rh factor and autoimmune diseases. Immunosuppressant selective agents have in time superseded the use of cytotoxic nonspecific agents (azathioprine and cyclophosphamide). Many immunosuppressant treatments are made of azathioprine in association with cyclosporine and steroids, therefore some of the studies consider them altogether.

L04AA – Selective immunosuppressant drugs

Case reports

- Haagsma et al (1989), Bung and Molitor (1991), Baruch et al (1993), Baxi and Rho (1993), Chinayon and Sakompant (1994), Dziatkowiak et al (1996), Morini et al (1998), and Coelho et al (2002). 9 healthy newborns exposed throughout pregnancy to combined immunosuppressant (azathioprine +/- cyclosporine + prednisone) for maternal transplantation (renal or liver or heart or heart-lung).

Control studies without controls

- Davison and Lindhemeier (1987), Registry of the European Association for Dialysis and Transplantation: 6 congenital anomalies (plagio-cephaly with cerebral impairments; mitral cardiopathy, bilateral talipes equinovarus; cerebral paralysis and hemorrhage in a couple of twins; hypospadias) out of 100 newborns exposed to immunosuppressant therapy.
- Kraemer-Hansen et al (1990): 17 exposures throughout pregnancy to combined immunosuppressant drugs (azathioprine +/- CSA + prednisone). 3 miscarriages, 3 VIP, 8 healthy newborns and 1 infant showing persistent ductus arteriosus.
- Muirhead et al (1992), Berardinelli et al (1992), Oyarzun et al (1993), Wagoner et al (1993), Haugen et al (Norway 1973-1991) (1994), Wong et al (New Zealand 1972-1992) (1995), and Troche et al (1997): 128 healthy newborns exposed throughout pregnancy to combined immunosuppressant drugs (azathioprine +/- CSA + prednisone) for maternal transplantation (renal or heart).
- Wu et al (1998): 23 healthy newborns exposed throughout pregnancy to combined immunosuppressant drugs (azathioprine, CSA, tacrolimus and steroids).
- Toledano Cuevas et al (1999): 32 exposures throughout pregnancy to combined immunosuppressant drugs (azathioprine +/- CSA + prednisone). 4 miscarriages, 27 healthy newborns, 1 newborn deceased with nonspecified multiple congenital anomalies.
- Willis et al (2000): 48 exposures throughout pregnancy to combined immunosuppressant drugs (azathioprine + prednisolone or CSA + prednisolone). 44 healthy newborns, 4 had anomalies of the urinary tract.
- Miniero et al (2002): 56 exposures throughout pregnancy to combined immunosuppressant drugs. 20 abortions (37.7%), 36 healthy newborns (13 CSA + steroids, 11 azathioprine+ tacrolimus + steroids, 9 azathioprine + steroids, 2 tacrolimus + steroids, 1 azathioprine + tacrolimus + steroids) 20 of which (55.6%) premature.
- Nagy et al (2003): 38 exposures throughout pregnancy to combined immunosuppressant drugs comprehending CSA or tacrolimus. 4 abortions, 10 VIP and 24 healthy newborns

Retrospective cohort studies with internal controls

- Sgro et al (2002), Toronto Renal Transplant Program: 44 newborns exposed to immunosuppressant therapy (26 to CSA + azathioprine + prednisone; 13 to azathioprine + prednisone; 5 to CSA + prednisone) and as many controls provided by Motherisk Program. There were 4 stillbirths and 1 newborn with multiple defects among the exposures vs. no cases among controls.

- Bar et al (2003): 48 exposures throughout pregnancy to combined immunosuppressant drugs comprehending azathioprine and/or CSA and/or tacrolimus and/or prednisone; as many nonexposed controls born to women with IRC. There were 2 newborns with major congenital anomalies (4.2%) (hypospadias and pulmonary anomaly) and 10 had minor malformations (20.8%) among exposures, vs. 2 newborns with major congenital anomalies (4.2%) and 8 with minor malformations (16.6%) among controls.

Prospective cohort studies with internal controls

- Crawford et al (1993), TIS California: 21 newborns to transplanted women (13 renal and 4 liver), exposed throughout pregnancy to CSA and prednisone and in 7 cases also to azathioprine. 70 controls born to women who had taken moderate quantities of alcohol during pregnancy. 2 newborns with congenital defects (emi-hypertrophy, hypoplasia of thumbs) in exposures vs. 0 in controls.

Cyclosporine (CSA) – L04AA01

Cyclic polipeptide having a molecular weight of 1202.64. In experimental models it causes immunosuppression inhibiting production and releasing of interleukins 2 and of other linfochins from T-helper cells with reversible effects. It is available in the USA since 1978.

Systematic review

- Bar Oz et al (2001): systematic good-quality review of literature through Medline and other sources to identify cohort studies with at least 10 exposures and clear information about the most important outcomes (malformations and low neonatal weight). Here are the results:
 - prevalence of congenital anomalies in 15 studies = 4.1% (CI 95%: 2.6-7.0). (Scantlebury et al 1990, Aichberger et al 1993, Crawford et al 1993, Framarino di Malatesta et al 1993, Ville et al 1993, Radomski et al 1995, Sabagh et al 1995, Barrou et al 1998, and Wu et al 1998), 6 out of the 15 studies were cohort ones, for a total of 410 exposures, with controls born to mothers transplanted, not treated with CSA (Muirhead et al 1992, Armenti et al 1994, Haugen et al 1994, Talaat et al 1994, Nojima et al 1996, and Bererhi et al 1997) OR for congenital anomalies = 3.8; IC 95%:0.8-19.6.
 - prevalence of prematurity in 10 studies = 56.3% (IC 95%: 37.8-74.7) (Scantlebury et al 1990, Aichberger et al 1993, Ville et al 1993, Sabagh et al 1995, Barrou et al 1998, Wu et al 1998), 4 out of the 10 studies were cohort ones for a total of 379 exposures with controls exposed to transplanted mothers not treated with CSA (Muirhead et al 1992, Haugen et al 1994, Radomski et al 1995, and Nojima et al 1996) OR for preterm birth = 1.5; IC 95%: 1.0-2.3.
 - prevalence of low weight at birth in 5 studies = 43.0 (IC 95%: 22.8-63.3) (Aichberger et al 1993, Ville et al 1993, Radomski et al 1995, and Wu et al 1998). 1 cohort for a total of 314 exposures with controls of infants born to transplanted mothers not treated with CSA (Nojima et al 1996). OR for low neonatal weight = 1.6; IC 95%:1.0-2.4.

Case reports

- Many healthy newborns have been reported, born to mothers treated with cyclosporine generally associated with steroids and/or other immunosuppressant drugs for renal, cardiac or hepatic transplant or else for the treatment of LES, in single reports (Jacobs and Dubovski 1981, Deeg et al 1983, Lewis et al 1983, Klintmolm et al 1984, Endler et al 1987, Calne et al 1988, Derfler et al 1988, Lowenstein et al 1988, Pickrell et al 1988, Williams et al 1988, Ziegenhagen et al 1988, Burrows et al

1988, Gunter et al 1989, Jonville et al 1989, Castelobranco et al 1990, Gunter et al 1990, Arellano et al 1991, Doria et al 1992, Ville et al 1992, Carmona et al 1993, Baxi e Rho 1993, Hussein et al 1993, Scott et al 1993, Shaheen et al 1993, Krayenbuhl et al 1994, and Pietrzak et al 1996). Congenital anomalies or tumors have been referred by:

- ☞ Pujals et al (1989): 1 newborn exposed to CSA throughout pregnancy (renal transplant) showing hypoplasia of the leg and of the right foot. Authors suggest that the cause of such a bone malformation should be the blockage made by cyclosporine on interleukin 2 – lymphocytic, that appears to play a role in the differentiation of osteoclasts.
- ☞ Roll et al (1977): 1 newborn exposed throughout pregnancy to CSA and prednisolone who at the age of 2 years has developed hepatoblastoma.

Prospective cohort study without controls (not taken in consideration in the systematic review because published later)

- Little et al (2000): 29 exposures throughout pregnancy to CSA. 4 miscarriages, 2 intrauterine deaths, 23 healthy newborns.

Feto-neonatal effects: reduced intrauterine growth (Pickrell et al 1988, Derfler et al 1988, Varghese et al 1988, Williams et al 1988, Crawford et al 1993, Rowemeier et al 1993, and Armenti et al 1994) not confirmed by Bar Oz et al (2001) in their meta-analysis. Prematurity (Little et al 2000), hypocalcemia (Kraemer-Hansen et al 1990); there were no differences between the group of exposed and that of controls as far as clinical immunologic status (Di Paolo et al 2000) and neurobehavioral development (Rieder et al 1997).

Conclusions: We have a large number of reported cases (about 500 exposures) of women who have used cyclosporine in pregnancy. There is no evidence of increased congenital defects. The problem of an increase in prematurity and reduced intrauterine growth is to be assessed in consideration of the illness and the attendant therapies usually employed in women who have had an organ transplant. The reported single case of hepatoblastoma should be considered and evaluated in the future.

Tacrolimus (FK-506) – L04AA05

This is a macrolide obtained from *Streptomyces* and used along with other drugs as an immunosuppressant in transplant patients. It inhibits calcineurin. It is available in Italy since 2001.

Literature review

- Kainz et al (2000 a-b) literature review of single cases both published and not published, including those of the pregnancy registry after organ transplant, of 100 pregnancies of 84 mothers exposed to tacrolimus: 12 miscarriages, 12 VIP, 1 stillbirth, 2 neonatal deaths, and 68 newborns 4 of whom with congenital anomalies (meningocele + urogenital defect; polycystic kidney; alcoholic embriopathy; ear defect+PS+hypospadias). Prematurity 59%.

Case reports

- Vyas et al (1999): 2 twins, 1 of whom died, exposed throughout pregnancy to tacrolimus (renal transplant) with dilated cardiomyopathy.
- Lovell et al (2003): 49 exposures to tacrolimus, 1 of whom died with nonspecified congenital anomalies.

Conclusions: We have found lots of cases (about 200 exposures) of women treated with tacrolimus in pregnancy, reported by different authors and by the Registry of Pregnancies of the manufacturer (Davison 2002). There is no evidence

of increased congenital malformations. An increase in the number of preterm births and of low-weight newborns has been documented.

Sirolimus – L04AA10

This is a macrolide that can inhibit the activation and proliferation of kitokins stimulating T-lymphocytes. It is used as immunosuppressant along with other drugs in transplant patients. 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.

Leflunomide – L04AA13

This is an inhibitor of pirimidin biosynthesis, used in the treatment of rheumatoid arthritis. It interferes with DNA and RNA synthesis. Its emi-life is of two weeks. 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.

Cohort studies without controls

- Brent (2001) reports data collected by the manufacturer: of 30 exposures, 27 VIP and 3 newborns whose outcome was unknown.

Conclusions: There are no specific studies relevant to the use of leflunomide in pregnancy, apart from the 30 exposures above mentioned. Other available information concerns its teratogenicity on animals. Some of the studies on experimental animals show congenital anomalies increase (anophthalmia/microphthalmia and hydrocephalous) in rats treated with 15 mg/kg/day (a toxic dose for the mother and lethal for the fetus). A dose as high as 10 mg/kg/day (the equivalent of a human dose) cause an increase in vertebral changes when administered to rabbits, while doses of 1 mg/kg/day it is not teratogenic in rabbits or rats. It is not easy to interpret such data.

L04AX – Other immunosuppressant agents

Azatioprine – L04AX01

This is an imidazole derivative of 6-Mercaptopurin. The most common toxic effect is dose-dependent and represented by myelosuppression. Patented in 1962.

Case reports

- Gevers et al (1971), Saarikoski and Seppala (1972), Sharon et al (1974), Symington et al (1977), Baruch et al (1993), Shigenobu et al (1993): 18 healthy newborns exposed in the first trimester of pregnancy to azatioprine.
- Williamson and Karp (1981): 1 newborn exposed throughout pregnancy to azatioprine and prednisone for maternal LES, had pre-assial polydactily of the right hand.
- Rasmussen et al (1981): 5 exposures in pregnancy: 4 healthy newborns, 3 of whom with signs of neonatal asphyxia, and 1 newborn with interventricular septum of heart. One newborn had granulocytopenia.

Cohort studies without controls

- Golby (1970), Penn et al (1971), Sciarra et al (1975), Marushak et al (1986), Haagsma et al (1989), Alstead et al (1990), Brown et al (1991), Ramsey-Goldman et al (1992), Baxi e Rho (1993), Wagoner et al (1994), Haugen et al (1994), Martinez-Rueda et al (1996), Kallen (1998), Bar et al (2003): about 250 newborns exposed since the first trimester of pregnancy to azatioprine both for

maternal transplant and for LES and inflammatory intestinal disease. Neither risk increase of congenital anomalies nor specificity of defects has been shown.

Feto-neonatal effects: suprarenal failure in newborns exposed to azathioprine and prednisone (Davison et al 1976, Penn et al 1971, Lower et al 1971); thrombocytopenia and leukopenia (Gevers et al 1971, Penn et al 1971, Lower et al 1971); pancytopenia, spinal cord aplasia, thymic dysplasia, and severe lymphopenia (De Witte et al 1984); prematurity (Armenti et al 2002).

Conclusions: None of the studies that we have been able to find in literature suggest an increase in the reproductive risk following an exposure to azathioprine in the first trimester of pregnancy. It is not clear whether neonatal emato-immunologic effects should be specifically attributed to azathioprine or to other drugs used in association with azathioprine, or else to the illness.