

H – SYSTEMIC HORMONE PREPARATIONS, BUT SEX HORMONES

H01 – Hypophyseal, hypothalamic and analog hormones

H01A – Hormones of the hypophysis anterior lobe and analogous hormones

H01AA – ACTH

Tetracosactide – H01AA02

This is a synthetic polypeptide containing the first 24 amino acids of ACTH and acting as adrenocortical stimulant. It is 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.

Feto-neonatal effects: There are no adverse effects in newborns exposed in the second half of pregnancy (Potert, 1962, Aral et al 1972). Theoretical risk of neonatal adrenaline impairment due to drug intake in the latest weeks of pregnancy should be considered.

Conclusions: Despite the lack of studies relevant to the first trimester of human pregnancy, in case of exposure reproductive risk-increase on population background is not likely. Pharmacological characteristics should in fact be considered, and the lack of reported anomalies over the long period of commercialization. Prescription over pregnancy is presumably rare, nonetheless to be taken in consideration, and, finally, teratogenic effects in laboratory animals have not been found (records provided by manufacturer for registration, not available in database). Due to the activity of the drug adrenocortical function should be thoroughly checked in newborns exposed to high doses.

Somatropin – H01AC01

It is available in Italy since 1988.

Case report

- Muller et al (1995): 1 healthy newborn exposed in the first trimester

Prospective cohort studies without controls

- Wiren et al (2002): 12 healthy newborns of 8 women suffering from pituitary defect exposed in the first and second trimester.

Conclusions: In case of exposure an increase in population-based reproductive risk is not likely, in spite of the almost total lack of data concerning the use of somatropin in human pregnancy. Its pharmacological characteristics, the failure to report anomalies over the long period of commercialization and the absence of data on the teratogenic action on laboratory animals should be considered (records provided by manufacturer for registration, not available in database).

H01B - Hormones of hypophysis posterior lobe

Desmopressin (DDAVP) – H01BA02

This is a synthetic polypeptide, vasopressin analog. It is available in Italy since 1979.

Systematic review of case report

- Ray (1998): in the systematic review from 1976 to 1997 twenty issues have been found pointing out one or more cases of exposures. An overall of 49 newborns had been exposed to an average intranasal dose of 29 µg (ranging between 7.5 and 100 µg) at various stages in pregnancy (41 also during the first trimester) to treat maternal diabetes insipidus. Two cases of Down syndrome (not attributable to the treatment) have been included in this review, and a cardiopathy and also a diabetes insipidus occurred at 18 months of age.

Prospective cohort studies

- Kallen et al (1995): Swedish MBR. 29 exposures throughout pregnancy, 1 single newborn with cardiac defect (DIV and patent ductus arteriosus). This is the sole cohort study, not included in the review by Ray (1998).

Feto-neonatal effects: no adverse effects have been reported in exposures during the second half of pregnancy and at birth (El-Hennawy et al 2003, Perez-Barrero et al 2003).

Conclusions: We have found only limited studies concerning the use of desmopressin in human pregnancy, and they do not show an increased population-based reproductive risk.

H01C – Hypothalamic hormones

Gonadorelin (gonadotropin releasing hormone: GnRH) – H01CA01

This is an ovulation stimulant, a synthetic hypothalamic decapeptide stimulating the hypophysis to produce synthesis and release of FSH and LH. Thoroughly used in the treatment of female infertility (Al-Inany and Aboulghar 2002). It is available in Italy since 1990.

Case report

- Bogehelman et al (1982): one GnRH induced pregnancy generated a triplet birth.
- Miller et al (1984): seven GnRH induced pregnancies generated 4 healthy newborns and 3 spontaneous abortions
- Hurley et al (1984): all nine GnRH induced pregnancies generated healthy newborns.

Cohort studies without control

- Wilshire et al (1993): of 18 pregnancies treated with GnRH antagonists, 5 miscarriages (28%), 1 missed labor at week 20 following cervical incontinence and 12 healthy infants.

Conclusions: We have not been able to find specific studies concerning the outcomes of pregnancies treated with gonadorelin or studies on inadvertent exposure during the early weeks of pregnancy. General experience suggest that gonadorelin intake be not responsible for an increased population-based reproductive risk (Tarlantzis and Bili 2004).

H01CB – Antigrowth hormone

Octeotide – H01CB02

This is a long-acting octapeptide with actions mimicking those of somatostatin, used for the treatment of symptoms associated with carcinoid tumors and endocrine tumors, usually involving the pancreas, and for the treatment of polycystic ovary syndrome. It is available in Italy since 1989.

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

Case report

- Landolt et al (1989), Montini et al (1990), Colao et al (1997), Paiva et al (1998): 5 healthy newborns exposed in the first trimester.
- Herman-Bonert et al (1999): 1 healthy newborn exposed at conception
- Caron et al (1996): 1 healthy newborn exposed from conception to the first month and from the 6th to the 8th month (birth)
- Takeuchi et al (1999), Mozas et al (1999), Neal (2000), Hierl et al (2000), Fassnacht et al (2001), Blackhurst et al (2002): 7 healthy newborns exposed throughout pregnancy, except for the case described by Mozas et al (1999), exposed at the 6th month only.

Lanreotide – H01CB03

This is a synthetic analog of somatostatin. 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.

Case report

- De Menis et al (1999): 1 healthy newborn exposed all-over the first month of pregnancy.

H01CB class conclusions: We have been able to find only few case reports in literature concerning cases of exposure to antigrowth hormones in human pregnancy, and none of them suggesting a teratogenic effect. In case of exposure a lack of teratogenic effects in laboratory animals should be considered (records provided by manufacturer for registration, not available in databases). In consideration of the limited information on the drug, this must be used extremely carefully.

H01CC – Releasing hormones of gonadotropin antagonists

Ganirelix – H01CC01

This is a third generation synthetic antagonist of GnRH, used as ovulation stimulant. It is available in Italy since 2000.

Case report

- Beckers et al (2003): 1 healthy newborn of a pregnancy treated with ganirelix.

Cohort studies without controls

- Olivennes et al (2001): 73 newborns of 67 pregnancies. Spontaneous abortions: 9%. Neonatal weight <2,500 g: 8.7% in single pregnancies (46) and 54% in multiple pregnancies (13). 1 newborn with Beckwith-Wiedmann syndrome (onphalocele and macroglossia), 7 minor defects in 5 newborns.

Prospective cohort studies with internal controls

- Boerrigter et al (2000): of 474 IVF pregnancies, 432 newborns treated with ganirelix (75.9% of single births, 21.2% twin births and 2.9 % triplet births). 184 newborns treated with other GnRH antagonists (67.9% single births, 26.9% twin births and 5.2% triplet births). There was no difference in the incidence of spontaneous abortion after week 16 of gestation. The incidence of major congenital anomalies was of 4.5% in the group treated with ganirelix vs. 3.3% of those treated with other GnRH (OR = 1.4; CI 95%: 0.5-3.5).

Cetrorelix – H01CC02

This is an antagonist of the hormone releasing luteinizing hormone (LHRH). It controls secretion of gonadotropins (LH and FSH) inhibiting pituitary secretion by means of a dose-dependent mechanism. It is used for IVF (Olivennes et al 2003). It is available in Italy since 1999).

Cohort studies without controls

- Ludwig et al (2001): of 234 cetrorelix induced pregnancies for IVF, 179 life births. The incidence of congenital anomalies among life births, stillbirths and abortions = 3.1%.

H01CC class conclusions: Every available study in literature, the large employment of these drugs as ovulation stimulants and the failure to report teratogenic effects in laboratory animals suggest that they are not causative of an increased population-based reproductive risk.

H02 – Systemic corticosteroids

H02AA – Mineralcorticoids

Desoxicortone – H02AA03

This steroid hormone is naturally produced by adrenal cortex. It helps sodium retention and potassium elimination. It has no glucocorticoid activity. Patented in 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.

Conclusions: We have not been able to find any specific studies in literature concerning the use of desoxicortone in human pregnancy and the sole possible evaluation can therefore be made associating it with other steroids.

H02AB – Glucocorticoids

These are steroids secreted by adrenal cortex (cortisol) or else made of synthetic compounds. They have a wide and complex activity range and their therapeutic employment is therefore considerable. They differ from their potency and plasma half-life. The use of corticosteroids against preterm delivery reduces the incidence and the seriousness of respiratory distress syndrome in premature infants (Liggins and Howie 1972, Howie and Liggins 1977, Taeusch et al 1979, Crowley 1981, Committee on Obstetric Practice 2002).

All studies available in literature concerning their use in the first trimester of pregnancy mostly regard corticosteroids as a whole, with no particular distinction among various drugs.

Systematic review

- Park-Wyllie et al (2000): systematic review to make a metanalysis of the risk for malformations associated with systemic steroids (except for topics). Of 455 papers chosen following classical methods, 434 have not been included since they were reviews, case reports and like, 8 did not allow OR evaluation, 3 had studied a too small number of cases (<10 treated women). Only 10 studies have therefore been taken in consideration, published between 1962 and 1999: 6 cohort studies (Popert 1962, Warrell and Taylor 1968, Heinonen et al 1977, Mogadam et al 1981, Mintz et al 1986, Park-Willie et al 2000), 4 case-controls (Robert et al 1994, Czeizel and Rockenbauer 1997, Rodriguez-Pinilla and Martinez-Frias 1998, Carmichael and Shaw 1999). They had been treated for various reasons (i.e. asthma, SLE, intestinal inflammatory disease), dosage was hardly reported, the treatment period was first trimester at least. Cumulative OR in cohort studies for major malformations was usually = 3.0 (CI 95%: 1.1-8.5). Of 15 malformations observed in the studies 3 cleft palate were highlighted (3 out of 390 exposures vs. none out of 708). Cumulative OR in case-control studies for facial schisis following first trimester exposure = 3.4 (CI 95%: 2.0-5.7) with no particular distinction between cleft palate and cleft lip. OR was not heterogeneous in both cases.

Case report

- Kraus (1975): 1 newborn, exposed throughout pregnancy to prednisone and cortisone with bilateral cataract.

Cohort retrospective studies with internal controls

- Rosa (1993), Michigan MSS: of 222 first trimester exposures to methyl prednisolone, 14 newborns had major defects, 9 expected. RR = 1.6 /CI 95%: 0.9-2.6); of 143 first trimester exposures to prednisolone, 11 newborns had

major defects, 6 expected: RR = 1.8 (CI 95%: 0.9-3.3); of 236 first trimester exposures to prednisone, 11 newborns had major defects, 10 expected: RR = 1.1 (CI 95%: 0.5-2.0).

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

- Kallen and Otterblad Olausson (2003), Swedish MBR: cases = 5,015 newborns with cardiovascular abnormalities, 20 of which exposed to systemic corticosteroids in the first trimester, 577,730 controls among which 2,132 exposures. OR for cardiovascular abnormalities = 1.1 (CI 95%: 0.7-1.7).
- Kallen (2003), Swedish MBR: cases = 1,044 newborns with labial non-syndromic cleft palate, 7 of which exposed in the first trimester to systemic corticosteroids, 576,873 controls, among which 2,050 exposures. AOR = 1.0 (CI 95%: 0.8-4.0).

Case-control studies, specific

- Pradat et al (2003), MADRE database: case-control study with controls showing other malformations. Cases = 645 cleft lip (palate) and 304 cleft palate vs. 10,168 controls. OR following systemic steroids for oral schisis (7 cases) = 2.6 (CI 95%: 1.2-5.7) for cleft palate (2 cases) = 1.2 (CI 95%: 0.3-4.9).

Betamethasone - A07EA04 – C05AA05 – D07AC01 – D07BC01 – D07CC01 – D07XC01 – **H02AB01** – R01AD06 – R03BA04 – S01BA06 – S01BB04 – S01CA05 – S01CB04 – S02BA07 – S03BA03 – S03CA0

It is a desamethasone isomer. Patented in 1961. For its use by inhalation, see R03BA04.

Desamethasone – A01AC02 – C05AA09 – D07AB19 – D07CB04 – D07XB05 – D10AA03 - **H02AB02** – R01AD03 – R01AD53 – S01BA01 – S01CA01 – S01CB01 – S02BA06 – S02CA06 – S03BA01 – S03CA01

It is used in the first trimester in the treatment of virilization associated to lipoid congenital adrenal hyperplasia, to impede maternal adrenal activity. Patented in 1970.

Fluocortolone – C05AA08 – D07AC05 – D07BC03 – D07CC06 - **H02AB03** – S01CA04

Patented in 1967.

Methyl prednisolone – D07AA01 – D07AC14 – D07CA02 – D10AA02 - **H02AB04** – H02BX01 – S01CA08

Patented in 1957.

Prednisolone – A01AC54 – A07EA01 – C05AA04 – D07AA03 – D07BA01 – D07CA03 – D07XA02 - **H02AB06** – R01AD02 – R01AD52 – S01BA04 – S01BB02 – S01CA02 – S01CB02 – S02BA03 - S02CA01 – S03BA02 – S03CA02 – V03AB05

This is the active metabolite of prednisone. Placenta can oxidize it into prednisone or cortisone. It reaches fetal circulation at a concentration 8-10 times lower than maternal. Patented in 1954.

Prednisone – A07EA03 – **H02AB07**

It reaches fetal circulation at a concentration 8-10 times lower than maternal. Patented in 1952.

Triamcinolone – A01AC01 – D07AB09 – D07BB03 – D07CB01 – D07XB02 - **H02AB08** - R01AD11 – R03BA06 – S01BA05 – S02CA04

Patented in 1956.

Hydrocortisone - A01AC03 - A07EA02 - C05AA01 - D07AA02 - D07AB02 – D07AB11 – D07AC16 - D07BA04 - D07BB04 - D07CA01 - D07XA01 – **H02AB09** - R01AD60 - S02BA01 - S01BA02 - S01BB01 - S01CA03 - S02CA03 - S03CA04 – S01CB03

This cortisone derivative is a corticosteroid obtained by adrenal cortex. Patented in 1950.

Cortisone – H02AB10 – S01BA03

This stagnant corticosteroid is obtained by adrenal cortex and transformed into hydrocortisone by liver. It has been used in the treatment of hyperemesis of pregnancy. Patented in 1950.

Deflazacort H02AB13

This is a synthetic glucocorticoid, oxozalinic prednisolone derivative. It has a half-life of 2 hours. It has little adverse effects in bone metabolism and in calcium balance, and it has little hyperglycemic action. It is available in Italy since 1985.

H02AB class conclusions: Corticosteroids cause cleft palate in laboratory animals (Shepard 2001). Several case reports had suggested a possible association between steroids and oral schisis. Metanalysis by Park-Wyllie et al (2000) and the case-control study by MADRE database (Pradat et al 2003) point out a light risk increase as for oral schisis following systemic use of corticosteroids in the first trimester of pregnancy. Due to very low risk and scarce power of the studies it is impossible to tell weather the risk for cleft lip-cleft palate is different from the risk for cleft palate alone. The highest evaluation for absolute individual risk should be around 5 per thousand of oral schisis (as against a population-based risk of 1 per thousand). Given such consideration it is advisable during the early weeks of pregnancy to limit the use of systemic steroids to imperative cases. In case of exposure it is essential to point out the doubt, qualify and assess the risk. Newborns exposed during gestation should be furthermore surveyed, due to the possibility of a cataract (although the risk is very low). This is a well-known side effect of steroids in adults and clinical reports suggest that the newborn might suffer from cataract, too.

H03 – Thyroid therapy

H03AA – Thyroid hormones

Sodium Levothyroxine – H03AA01

It is a natural hormone (T4) produced by the mother and the fetus. Patented in 1953.

Case report

Mayer and Hemmer (1956): 1 newborn exposed throughout pregnancy with ocular defects.

Prospective cohort studies without internal controls

- Rosa (1993), Michigan MSS: of 554 first trimester exposures, 25 newborn had major defects, 24 expected (RR = 0.1; CI 95%: 0.7-1.5).

Sodium Liothyronine – H03AA02

This is a natural hormone (T3) produced by the mother and the fetus. Patented in 1953.

Prospective cohort studies with internal controls

- Heinonen et al (1977), CPP: of 34 exposures in the early 16 weeks, 1 newborn with congenital anomaly. (ARR for every type of malformation = 0.6; CI 95%: 0.1-4.4).

H03AA class conclusions: Levothyroxine and Liothyronine are recommended during pregnancy in the treatment of maternal hypothyroidism.

H03B – Antithyroid agents

The frequency of hyperthyroidism is of 1 out of 500 pregnancies (Mandel 1995). Antithyroids interfere with the incorporation of iodine processed by thyroglobulin, thus inhibiting the synthesis of thyroid hormones. Thiamides are mostly used to serve this purpose since they can alter the fetus thyroid functions after week 10 of gestation. Pituitary-thyroid axis, in fact, starts functioning since week 12-14 of gestation (Hobel 1980, Mandel 1955).

Case report and cohort studies without controls

- Hawe and Francis (1962), Herbst and Selenkow (1963 and 1965), Reveno and Rosenbaum (1964), Talbert et al (1970), Refetoff et al (1974), Mestman et al (1974), Ramsay (1976), Low et al (1978), Robinson et al (1979), Kock and Merkus (1983), Pekonen et al (1984), Jeffcoate and Bain (1985), Manfredini et al (1992). They all report the positive outcome of pregnancies treated with antithyroids.

Prospective cohort studies with internal controls

- Heinonen et al (1977), CPP: of 25 exposures in the early 16 weeks of pregnancy (16 to propyl-thio-uracile, 9 to methimazole, 1 to amethyltiouracile and 1 to iodotiouracile), 4 newborns had congenital anomalies. ARR for any type of malformations = 3.5 (CI 95%: 1.4-8.7).

H03BB – Imidazole derivative containing sulfur

Thiamazole (Methimazole) – H03BB02

This hormone antagonist belongs to thiamides. It is also an active metabolite of carbimazole. Patented in 1945.

Case report

- Zolcinski and Heimrath (1966): 1 newborn exposed in uterus at various stages of pregnancy with microsomia and talipes equinovarus.
- Milham (1986): has collected 9 case reports of newborns exposed to methimazole and carbimazole (methimazole is an active metabolite of carbimazole), showing scalp anomalies. Mujtaba and Burrow, 1975 reported 2 cases; Milham and Elledge, 1972 3 cases and Rosa, Cordero and Van Dijke (later published in 1987) respectively reported one case each as personal notice. Also Koo reported a further case of exposure to carbimazole.
- Kalb and Grossman (1986): 1 newborn exposed in the first trimester of pregnancy with scalp aplasia.
- Greenberg (1987): 1 newborn exposed throughout pregnancy showing choanal atresia, absence of nipples, a small area of alopecia, minor malformations and mental retardation.
- Farine et al (1988): 1 newborn exposed to methimazole in the first trimester of pregnancy and to propiltiouracile for the rest of pregnancy, had scalp defect.
- Tanaka et al (1989): 1 newborn exposed to methimazole during pregnancy had scalp defect.
- Dutertre et al (1991): 1 newborn exposed to carbimazole (methimazole being its active metabolite), with scalp aplasia.
- Martinez-Frias et al (1992): 1 newborn exposed to carbimazole (methimazole being its active metabolite), with scalp aplasia.
- Ramirez et al (1992): 2 newborns exposed throughout pregnancy showing esophageal atresia, tracheo-esophageal fistula and goiter.
- Manfredini et al (1992): 1 healthy newborn exposed between the beginning of pregnancy and the sixth month.
- Sargent et al (1994): 1 newborn exposed to a methimazole was showing scalp defect, absence of nipples and external ear defect.
- Mandel et al (1994): 1 newborn with scalp aplasia had been exposed prior to pregnancy until week 20.
- Vogt et al (1995): 1 newborn exposed throughout pregnancy had scalp aplasia.
- Hall (1997): 1 newborn exposed in the first 2 months of pregnancy had choanal atresia, retinal coloboma, right renal pelvis stasis, and minor facial dysmorphism.
- Johnsson et al (1997): 1 newborn exposed until the 18th week of gestation with choanal and esophageal atresia, tracheo-esophageal fistula and DIV.
- Wilson et al (1998): 1 newborn exposed to carbimazole (methimazole being its active metabolite), with bilateral choanal atresia, hypoplastic nipples and slow development.
- Rodriguez-Garcia (1999): 1 newborn exposed in the first period of pregnancy had bilateral renal agenesis.
- Clementi et al (1999): 1 newborn exposed prior to conception and until the seventh week of gestation had bilateral choanal atresia, esophageal atresia and tracheo-esophageal fistula, patent ductus arteriosus, bilateral convergent strabismus, severe psychomotor delay with tetraparesis, facial dysmorphisms and scalp defect.
- Martin-Danavit et al (2000): 1 newborn exposed throughout pregnancy with scalp aplasia, psychomotor delay, extra nipples, foot syndactyly, hypertrichosis, dystrophic and short ungual phalanxes.
- Barwell et al (2002): 1 newborn exposed to carbimazole (methimazole being its active metabolite), with bilateral choanal atresia
- Guignon et al (2003): 1 newborn exposed to carbimazole (methimazole being its active metabolite), with gastroschisis.
- Seoud et al (2003): 2 newborns to the same woman exposed after the 14th week of gestation, one showing esophageal atresia and tracheo-esophageal fistula and the other atresia of biliary ways.

Synthesis of case records

Author	Scalp defects/ Scalp aplasia	Choanal atresia	Esophageal atresia	Other anomalies
Milham 1985	9 cases			
Kalb e Grossman 1986	+			
Greenberg 1987	+	+		Nipples Hypo/aplasia, mental retardation
Farine et al 1988	+			
Tanaka et al 1989	+			
Dutertre et al 1991	+			
Martinez-Frias et al 1992	+			
Ramirez et al 1992			+	Goiter
Sargent et al 1994	+			Nipples hypo/aplasia
Mandel et al 1994	+			
Vogt et al 1995	+			
Hall 1997		+		Retinal coloboma; pelvis renal estasia; facial dysmorphisms
Johnsson et al 1997		+	+	DIV
Wilson et al 1998		+		Nipples hypo/aplasia, developmental delay
Rodriguez-Garcia 1999				Bilateral renal agenesis
Clementi et al 1999	+	+	+	Tetraparesis, facial dysmorphism, PDA
Martin-Danavit et al 2000	+			Extra nipples, psychomotor delay, hypertrichosis
Barwell et al 2002		+		
Guignon et al 2003				Gastroschisis
Seoud et al 2003			+	
Seoud et al 2003				Atresia of biliary ways

Cohort studies without controls

- Van Dijke et al (1987): 24 exposures to methimazole and carbimazole among 48,057 women. None of the newborns had scalp aplasia.
- Kriplani et al (1994): 27 newborns exposed to methimazole and carbimazole. None of the newborns had scalp aplasia.
- Wing et al (1994): 36 newborns exposed to methimazole and carbimazole. None of the newborns had scalp aplasia.

Retrospective cohort studies with internal controls

- Rosa (1993), Michigan MSS: 5 newborns exposed in the first trimester, 1 newborn with hypospadias, none expected.
- Momotani et al (1984): he studied the offspring of 4 groups of mothers with hyperthyroidism (Greaves syndrome) to assess the incidence of major malformations. The incidence of malformations in the offspring of mothers treated with methimazole was similar to the incidence of non-treated mothers (2/243 vs. 4/400). Both groups of exposed infants were showing onphalocele and ear lobe defect. Interesting data rose from the thyroid function test carried out during pregnancy: the incidence of malformations in the offspring of hyperthyroid mothers was higher compared to the incidence of euthyroid ones regardless of the type of treatment (5/167 vs. 1/476) RR = 14.3 (CI 95%: 1.7-

121.1). Despite the low incidence of defects, this study clearly remarks that hyperthyroidism per se is a risk factor for congenital anomalies.

- Di Gianantonio et al (2001), ENTIS: 288 exposures, 241 of which with complete follow-up (84%) and, among them, 204 newborns. Controls: 1,089 newborns exposed to unanimously reckoned nonteratogenic agents. 8 exposed newborns had major malformations (craniosynostosis + hypospadias; malformation of the interventricular septum of heart; choanal atresia; scrotal hypospadias, spina bifida in twin birth; scrotal hypospadias + hemivertebra; atrioventricular canal and esophageal atresia), vs. 23 newborns among controls. RR = 1.6 (CI 95%: 0.7-3.5). Minor defects, such as scalp minor anomalies, may have been under-ascertained since their ascertainment was based on mother interviews.

Feto-neonatal effects: no difference was noticed in the IQ of the offspring exposed in pregnancy to methimazole (Eisenstein et al 1992, Azizi et al 2002); transitory hypothyroidism (Refetoff et al 1974, Low et al 1978, Burr 1981, Burrow 1985), hypothyroidism and cretinism (Hawe and Francis 1962).

Conclusions: Methimazole, as well as other anti-thyroid drugs, interferes with the development of thyroid causing fetal goiter, hypo- and hyperthyroidism (Hawkins 1983). It can also be causative of an actual syndrome (embryopathy) where scalp defects are the minor and most frequent anomalies, whereas esophageal atresia is the major and rarest ones. The identification of such a syndrome, with variable clinic anomalies, is based on the accurate description of some cases with a more comprehensive number of clinic anomalies (Clementi et al 1999). Further cases with a variable or minimal description of anomalies (see the above complete review) support this thesis and a cohort study of 204 newborns (Di Gianantonio et al 2001), 2 of which were showing characteristic malformations of the syndrome (choanal and esophageal atresia). It is impossible to exactly assess the incidence of the syndrome that can nevertheless be estimated around 1 % of the exposures (from the data by Gianantonio et al 2001). Given the relatively rareness of the syndrome it is understandable that some cohort studies are not enough powerful to detect it. In order to explain the issue a cohort study or a case-control study is needed, relevant to the specific anomalies of the syndrome. The study should have enough power to separate the outcomes of the drug from those of the illness, since the doubt is not yet dispelled that the syndrome be associated to illness. In conclusion, women with hyperthyroidism should not be treated with methimazole and carbimazole and, in case of exposure, the risk range and its specificity must be pointed out. Targeted echographies can detect major defects such as esophageal atresia. In the field of prospective advice to women suffering from hyperthyroidism it is useful to remind that propiltiouracile, not marketed in Italy, is considered a drug of choice (Kock and Merkus 1983, ACOG 1993, Mandel et al 1994, Atkins et al 2000) despite of the fact that it might cause fetal goiter (Masiukiewicz and Burrow 1999) and transitory hypothyroidism in 1-5% of the exposed newborns (Davis et al 1989, Becks and Burrow 1991, Masiukiewicz and Burrow 1999).

H03BC – Perchlorates

Potassium perchlorate – H03BC01

It is an antithyroid "ionic inhibitor", as far as it interferes with the thyroid captation of iodide ions that cannot therefore be employed in the production thyroglobulin.

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 concerning the use of potassium perchlorate in human pregnancy. This being an antithyroid agent it is capable of changing thyroid functions of the fetus after the 10th week of gestation and determining hypothyroidism and/or goiter.

H04A – Pancreatic hormones

H04AA – Glycogenolytic hormones

Glucagon – H04AA01

This is a hyperglycemic hormone, naturally produced by the pancreas, but it can also be produced synthetically. It does not cross the placenta. It is available in Italy since 1991.

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

Studies on laboratory animals

- Scaglione (1960): fetal cataract in rats at 20-200 µg.
- Tuchman-Duplessis and Mercier-Parot (1962): glaucoma in rats at 300 µg, microphthalmia and skeletal defects at 400-500 µg.

Conclusions: This agent does not cross the placenta, but its hyperglycemic effects on the mother may be a risk for the fetus.

H05 – Calcium-homeostatic agents

H05B – Parathyroid hormones

Calcitonin – H05B01

It is available in Italy since 1978.

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

Studies on laboratory animals

- Fuchigami et al (1986), Ito et al (1988), Takahashi et al (1993), Kawanishi et al (1994), King et al (1994): nonteratogenic in rats and rabbits at dosages 1-2.5 and 1-10 times the human therapeutic dose, respectively.

Elcatonin – H05B04

It is available in Italy since 1986.

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

H05B class conclusions: There are no specific studies in literature concerning the use of parathyroid hormones in human pregnancy, since such drugs are employed in the treatment of pathologies not so frequent in fertile women. In case of exposure it should be reminded that there is a lack of reported anomalies over the long period of commercialization and teratogenic effects in laboratory animals have not been found (records provided by manufacturer for registration, not available in database).