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Title: EUROmediCAT signal detection: an evaluation of selected congenital anomaly-medication associations

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Competing interests

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Structured summary

Aim: To evaluate congenital anomaly (CA)-medication exposure associations produced by the new EUROmediCAT signal detection system and determine which require further investigation.

Methods: Data from 15 EUROCAT registries (1995-2011) with medication exposures at the chemical substance (5th level of Anatomic Therapeutic Chemical classification) and chemical subgroup (4th level) were analysed using a 50% false detection rate. After excluding antiepileptics, antidiabetics, antiasthmatics and SSRIs/psycholeptics already under investigation, 27 associations were evaluated. If evidence for a signal persisted after data validation, a literature review was conducted for prior evidence of human teratogenicity.

Results: 13/27 CA-medication exposure signals, based on 3-89 exposed cases, passed data validation. There was some prior evidence in the literature to support 6 signals (gastroschisis and levonorgestrel/ethinylestradiol (OR 4.10, 95% CI 1.70-8.53; congenital heart disease/pulmonary valve stenosis and nucleoside/tide reverse transcriptase inhibitors (OR 5.01, 95% CI 1.99-14.20/OR 28.20, 95% CI 4.63-122.24); complete absence of a limb and pregnen (4) derivatives (OR 6.60, 95% CI 1.70-22.93); hypospadias and pregnadien derivatives (OR 1.40, 95% CI 1.10-1.76); hypospadias and synthetic ovulation stimulants (OR 1.89, 95% CI 1.28-2.70). Antipropulsives produced a signal for syndactyly while the literature revealed a signal for hypospadias. There was no prior evidence to support the remaining 6 signals involving the ordinary salt combinations, propulsives, bulk-forming laxatives, hydrazinophthalazine derivatives, gonadotropin releasing hormone analogues and selective serotonin agonists.

Conclusion: Signals which strengthened prior evidence should be prioritised for further investigation, and independent evidence sought to confirm the remaining signals. Some chance associations are expected and confounding by indication is possible.

What is already known about this subject

- There is insufficient information on the safety of the vast majority of medications when taken during pregnancy and more post-marketing surveillance of medication safety in pregnancy is needed
- Signal detection based on spontaneous adverse effect reporting is biased and incomplete.

What this study adds

- The EUROmediCAT database, comprising data from population-based EUROCAT congenital anomaly registries, can be used for systematic signal detection and signal strengthening.
- Our results strengthen 6 congenital anomaly-medication exposure signals in the literature
- We generated 7 new signals which require independent confirmation as some may be chance findings.

Introduction

Congenital anomalies (CAs), structural or functional abnormalities that are present from birth [1], are a major cause of infant mortality, childhood morbidity and long-term disability [2]. They are a diverse group of disorders of prenatal origin and can be caused by a wide range of factors such as genetics, environmental agents, medications and physical conditions [3–5]. While a number of antenatal medication exposures are known to cause CAs [6], there is insufficient information on the risks and safety for the vast majority of medications [7]. The critical period for most major CAs is during organogenesis, in the first trimester of pregnancy [8]. It has been estimated that 22-54% of pregnancies [9,10] are exposed to prescription medications, excluding vitamins and minerals, during this time period. As a result, the lack of information in relation to the safety of medication during human pregnancy is a serious public health problem [11].

Typically, eligibility criteria for premarketing clinical trials exclude high risk individuals such as pregnant women [12]. The evaluation of medication safety in human pregnancy therefore relies on post-marketing surveillance to detect medication safety signals [13]. As defined by the World Health Organisation (WHO), a signal refers to 'reported information on a possible causal relationship between an adverse event and a medication, the relationship being unknown or incompletely documented previously' [14].

Signals are detected when the observed number of reports is higher than expected for a particular medication-event combination [12,15]. Such statistical signals are frequently found because of the large number of comparisons made and do not necessarily mean that a causal association is present [12]. Even strong signals can

be generated by various forms of confounding [16] so once a signal is generated, signal strengthening and signal evaluation are necessary in order to reinforce or refute the potential signal [13,16,17]. While information on true medication safety signals should not be withheld from physicians and patients, false positive signals may cause substantial harm if they limit access to safe medications [17].

Traditionally signal detection has relied on national or international spontaneous reporting systems which pool reports of adverse medication events provided by healthcare providers, consumers and medication manufacturers [15]. Spontaneous report databases have a number of limitations such as under-, over- and duplicate reporting, limited information on concomitant medication or comorbidities and susceptibility to bias [12–14]. To overcome some of these limitations, programs have been initiated to make use of large data pools besides spontaneous reports such as healthcare databases and disease registries [13,18,19]. EUROmediCAT's population based reproductive pharmacovigilance system is based on the European Surveillance of Congenital Anomalies (EUROCAT) network. A statistical signal detection analysis was conducted using the EUROmediCAT central database to find highly statistically significant CA-medication exposure associations (see attached paper co-submitted to BJClinPharm). The aim of this paper is to describe the protocol used for evaluation of the signals produced by the EUROmediCAT statistical signal detection analysis, and to give the results of evaluation of 27 CA-medication exposure associations to determine which should be prioritised for further investigation. We do not report here signals belonging to four medication groups which were separately investigated as part of the EUROmediCAT project: antiepileptic medications, insulin/insulin analogues, antiasthmatic medications and selective serotonin reuptake inhibitors and psycholeptics [20–23].

Methods

Dataset and statistical signal detection analysis

EUROCAT registries record all cases of major CA seen, among live births, fetal deaths ≥20 weeks' gestation and termination of pregnancy for fetal anomaly (TOPFA) [24–26]. Births from 15 EUROmediCAT registries across 13 countries (1995-2011) were used to create a signal detection dataset, see supplementary table 1 [Ref. attached paper]. This included 14,950 infants with a CA, excluding genetic conditions[1] or isolated congenital dislocation of the hip, who were exposed to a medication in the first trimester, excluding folic acid, minerals, vitamins and/or topical medication [Ref attached paper co-submitted to BJClinPharm], coded to the Anatomic Therapeutic Chemical (ATC) classification system [27]. Data on maternal medication exposures are mostly obtained from prospectively recorded maternity records [28,29].

The signal detection methodology used is previously described [see attached article]. In brief a case-malformed control approach was used where cases of a specific CA subgroup [30] were compared to all other CAs in terms of exposure to each specific medication. The signal detection analysis was conducted using medications recorded at the 4th ATC level (chemical subgroup) and the 5th ATC level (chemical substance). Use of different ATC codes for the same medication and changes to ATC codes over time were taken into account. Medications with less than 3 exposed fetuses/babies were excluded from the analysis. Any registry with no exposures to the medication of interest, or cases of the CA of interest, were also removed from each analysis. Overall, 59 CA subgroups and 693 medication groups were tested,

[1] Chromosomal anomalies, genetic syndromes and skeletal dysplasias

resulting in 40,385 analyses. In order to limit the number of false positive associations multiple testing procedures were implemented, using a 50% false discovery rate (FDR), where the cut-off p value for associations at the 5th ATC level was 0.00040 and at the 4th ATC level was 0.0011 [Ref. attached article]. As the individual medications at the 5th ATC level all contribute to the 4th ATC level group, if an association arose at both the 4th and 5th ATC level the 5th ATC level association was taken as the result. This analysis produced 11 CA-medication exposure signals [Ref. attached article] which were from medication groups not already being investigated as part of the EUROmediCAT project [31] i.e. excluding antiepileptics, antidiabetics, antiasthmatics and SSRIs/psycholeptics.

A previous analysis of the same dataset without some of the analytic refinements reported here (such as the amalgamation of duplicate ATC codes) [32], and cut-off p values for associations at the 5th and 4th ATC level of 0.00048 and 0.0028 respectively, had identified an additional 16 signals. These original signals were included for further analysis as a comparison of the Odds Ratios (OR) and 95% CIs remained very similar between the original and revised analyses (Figure 1 and Table 1), and although the FDR p-value threshold was slightly higher, it is not the sole criterion for identifying a potential association of interest. When both sets of results were combined there were 27 CA-medication exposure signals. Results are given combined and separately.

Signal validation

Initially, the exposed cases for each of the 27 CA-medication exposure associations were validated, in terms of diagnosis, medication exposure, and timing of exposure, with the local registries.

The OR based on these validated data were then adjusted for confounding by registry i.e. where a registry may differ in both their (recorded) exposure proportion and (recorded) CA subgroup proportion in such a way as to produce artificial relationships between the exposure and outcome. Adjustment for registry was done by conducting a meta-analysis in STATA/SE 12.1 using the fixed effect Mantel–Haenszel method [33,34]. Continuity corrections were made as per the method by Sweeting et al. (2004) [35].

With the exception of chromosomal anomalies, most CAs are not strongly associated with maternal age [36]. However, gastroschisis, an abdominal wall defect, is associated with young maternal age [37] and it was necessary to adjust the gastroschisis-medication exposure association for maternal age. This was done by stratifying the meta-analysis by maternal age group [38], categorised as < 20, 20-24, 25-29, 30-34, 35-39 and 40+.

Those CA-medication exposure associations which persisted, when using validated data and adjusting for registry effects, were considered validated statistical signals.

Signal description

The validated statistical signals were then described in detail in terms of the signal ORs and 95% CIs, the adjusted ORs and 95% CIs using validated data, the number of exposed cases and the most prevalent concurrent medication exposures recorded among exposed cases. In addition, the statistically significant CA-medication exposure associations which failed to meet the FDR threshold (FDR <50%) but which involved the same medication, or 3rd ATC level, exposure were also noted.

Signal literature review

A literature review was then conducted, for the validated statistical signals, by searching REPROTOX, TOXBASE, the Developmental and Reproductive Toxicology Database (DART) and PubMed. For those signals at the 5th ATC level this involved searching initially for the specific medication and then for the 4th ATC level medication group. For signals at the 4th ATC level a literature review was conducted for both the medication group and each specific medication in the group. REPROTOX and TOXBASE were searched using the medication/group name alone. DART and PubMed were searched using the name of the medication/group combined with search terms for teratogen and CA, see Supplementary Document 1 for more detail. The reference lists of relevant articles were also searched. Cohort and case-control studies were of particular interest but case reports/series were also noted where available as the evidence was limited for some medications. The available published evidence was categorised according to the amount of evidence to support the signal in the human literature i.e. signal CA described in literature, teratogenicity leading to other CA described in the literature, or no evidence of teratogenicity in the literature. When the evidence was based on case reports/series or a single case-control or cohort study the published evidence was noted as minimal.

Ethical approval

Ethical approval for this study was provided by the University of Ulster Nursing Research Governance Filter Committee.

Results

Signal validation

Out of the 27 original CA-medication exposure associations 14 (7 from the original and 7 from the revised analysis) were not validated as independent signals: one was a duplicate signal as more than one formulation of the medication is available (the combined contraceptive levonorgestrel and ethinylestradiol); for 5 CA-medication exposure associations a proportion of the CA cases and/or first trimester medication exposures could not be verified so that the OR using validated data more than halved to less than 1.5; 8 CA-medication exposure associations were explained by confounding by registry.

This left 13 (9 from the original and 4 from the revised analysis) validated unique CA-medication exposure signals related to gastrointestinal medications (n=4), antihypertensives (n=1), female sex hormones (n=3), medications used in infertility treatments (n=2), antiretrovirals (n=2) and selective serotonin (5HT1) agonists (n=1).

Signal description

The 13 statistical signals were based on between 3 and 89 confirmed CA cases with first trimester medication exposures (Table 1).

Table 1 Description of validated signals

ATC code/s Medication/s and Congenital Anomaly	Signal OR (95% CI)	p value	Number of cases (confirmed 1st trimester exposures)	Mantel-Haenszel adjusted* OR using validated data (95% CI)	Most prevalent concurrent medication exposures among cases (n)	Significant positive medication-CA exposure associations not meeting FDR criteria (unvalidated§)
A02AD01 Ordinary salt combinations and cleft lip with or without cleft palate	2.38 (1.46-3.72)	0.00036	23 (21)	1.70 (1.06-2.72)	None (4), piperazine derivatives R06AE(2), other medications for peptic ulcer and gastro-oesophageal disease A02BX (2), paracetamol N02BE01 (2), cisapride A03AF02 (1)	A02AD01 and cleft palate (OR 2.65, 95% CI 1.49-4.42) A02AD01 and Anopthalmos/micropthalmos (OR 5.17, 95% CI 1.57-13.35) A02AB04 and polydactyly (OR 16.62, 95% CI 2.20-124.82)
A03FA Propulsives (metoclopramide, cisapride, domperidone, bromopride, alizapride, clebopride and itopride) and total anomalous pulmonary venous return‡	6.41 (1.89-17.46)	0.0021	5 (5)	10.49 (3.45-31.93)	None (10), levothyroxine sodium H03AA01 (2), omeprazole A02BC01 (1), prochlorperazine N05AB04 (1), promethazine R06AD02 (1)	None

A06AC Bulk-forming laxatives (ispaghula (psylla seeds), ethulose, sterculia, linseed, methylcellulose, triticum (wheat fibre), polycarbophil calcium, ispaghula combinations, sterculia combinations and linseed combinations) and anencephalus and similar‡	8.98 (2.29-25.53)	0.0015	4 (4)	6.38 (2.23-18.24)	None (2), amoxicillin J01CA04 (1), follitropin alfa G03GA05 (1), chorionic gonadotrophin G03GA01 (1), levonorgestrel and ethinylestradiol G03AA07 (1)	A06AC and ventricular septal defect (OR 2.69, 95% CI 1.34-5.21) A06AC and cleft lip with or without cleft palate (OR 3.37, 95% CI 1.16-8.10) A06AC and neural tube defects (OR 3.64, 95% CI 1.11-9.32) A06AD and club foot/talipes equinovarus (OR 2.21, 95% CI 1.09-4.09)
A07DA Antipropulsives (diphenoxylate, opium, loperamide, difenoxin, loperamide oxide, morphine combinations and loperamide combinations) and syndactyly‡	10.12 (2.42-32.05)	0.0013	4 (4)	6.41 (2.28-18.00)	None (3), nitrofurantoin J01XE01 (1)	None
C02DB Hydrazinophthalazine derivatives (dihydralazine, hydralazine, endralazine,	5.78 (1.39-22.81)	0.0077	5 (5)	2.78 (1.07-7.24)	None (3), methyldopa C02AB01 (2), diprophylline R03DA01 (1)	None

cadralazine) and Atrial septal defect (ASD)‡						
G03AB03 or G03AA07 Levonorgestrel and ethinylestradiol and gastroschisis‡	4.10 (1.70-8.53)	0.0013	8 (8)	2.95 (1.38-6.33)¥	None (6), trimethoprim J01EA01 (1), ibuprofen M01AE01 (1)	G03AB03 or G03AA07 and bladder exstrophy and/or epispadia (OR 7.05, 95% CI 1.36-23.2) G03AA09 and neural tube defects (OR 4.88, 95% CI 1.23-14.18) G03AA13 and CHD (OR 6.12, 95% CI 1.16-60.46) G03AA and congenital cataract (OR 3.47, 95% CI 1.09-8.54) G03AA and anencephalus and similar (OR 2.69, 95% CI 1.05-5.76)
G03DA Pregnen (4) derivatives (gestonorone, medroxyprogesterone, hydroxyprogesterone and	6.60 (1.70-22.93)	0.0035	5 (5)	7.60 (2.34-24.67)	None (3), estradiol combinations G03CA53 (1), estradiol G03CA03 (1)	G03DA04 and ASD (OR 1.38, 95% CI 1.12-1.68)

progesterone) and complete absence of a limb‡						G03DC and ASD (OR 1.79, 95% CI 1.09-2.82)
G03DB Pregnadien derivatives (dydrogesterone, megestrol, medrogestone, nomegestrol, demegestone, chlormadinone, promegestone and dienogest) and hypospadias‡	1.40 (1.10-1.76)	0.0036	91 (89)	1.51 (1.15-1.98)	None (59), drotravine A03AD02 (7), hydroxyprogesterone G03DA03 (6), aspirin B01AC06 (4), progesterone G03DA04 (3), A03AD02 (5)	G03DC and neural tube defects (OR 2.21, 95% CI 1.07-4.13) G03DC and limb reduction (OR 2.26, 95% CI 1.00-4.47)
						G03DB and congenital heart defects (CHD) (OR 1.39, 95% CI 1.19-1.61)
G03GB Synthetic ovulation stimulants (cyclofemil, clomifene and epimestrol) and hypospadias	1.89 (1.28-2.70)	0.00073	37 (36)	1.92 (1.35-2.74)	None (22), progesterone G03DA04 (4), chorionic gonadotropin G03GA01 (4), levothyroxine sodium H03AA01 (3), labetalol C07AG01 (2)	G03GA and laterality (OR 4.92, 95% CI 1.72-11.47) G03GA08 and ASD (OR 1.95, 95% CI 1.21-3.02) G03GA01 and congenital constriction bands/amniotic band (8.00, 95% CI 1.53-26.59) G03GA02 and neural tube defects (OR 3.12, 95% CI 1.19-6.98)

						G03GA04 and ventricular septal defect (OR 7.34, 95% CI 1.24-50.14) G03GA01 and bladder exstrophy and/or epispadia (OR 6.45, 95% CI 1.25-20.97)
L02AE Gonadotropin releasing hormone analogues (buserelin, leuprorelin, goserelin, triptorelin and histrelin) and laterality anomalies[‡$]	13.34 (2.52-45.08)	0.0021	3 (3)	9.09 (2.75-30.08)	follitropin alfa G03GA05 (2), chorionic gonadotrophin G03GA01 (2), urofollitropin G03GA04 (1), progesterone G03DA04 (1)	L02AE04 and severe CHD (OR 4.52, 95% CI 1.01-16.3)
J05AF Nucleoside and nucleotide reverse transcriptase inhibitors (zidovudine, didanosine, zalcitabine, stavudine, lamivudine, abacavir, tenofovir disoproxil, adefovir dipivoxil, emtricitabine, entecavir, telbivudine, clevudine) and congenital heart defects (CHD)	5.01 (1.99-14.2)	0.00012	18 (20)[#]	2.04 (1.17-3.55)[#]	None (8), protease inhibitors J05AE (8), ritonavir J05AE03 (4), lopinavir and ritonavir J05AE06 (3), sulfamethoxazole and trimethoprim J01EE01 (1), combinations of sulfonamides and trimethoprim, including derivatives J01EE (1)	J05AF and severe CHD (OR 3.53, 95% CI 1.15-9.22) J05AB11 and polydactyly (OR 7.69, 95% CI 1.38-28.46) J05AE03 and CHD (OR 5.92, 95% CI 1.05-60.21)

J05AF30 Combinations of nucleoside and nucleotide reverse transcriptase inhibitors and pulmonary valve stenosis	28.2 (4.63-122.24)	0.00039	3 (4) [#]	5.08 (1.83-14.07) [#]	Nucleoside and nucleotide reverse transcriptase inhibitors J05AF (3), protease inhibitors J05AE (2), nevirapine J05AG01 (1), non-nucleoside reverse transcriptase inhibitors J05AG (1), lopinavir and ritonavir J05AE06 (1), saquinavir J05AE01 (1)	
						J05AF30 and ASD (OR 6.08, 95% CI 1.03-25.55)
N02CC Selective serotonin (5HT1) agonists (sumatriptan, naratriptan, rizatriptan, almotriptan, eletriptan and frovatriptan) and congenital constriction bands/amniotic band‡	12.97 (2.46-43.53)	0.0022	3 (3)	15.58 (4.44-54.62)	ispaghula A06AC01 (1), 'other' anti-obesity medications A08AX (1), dalteparin B01AB04 (1), fluconazole J02AC01 (1), ibuprofen M01AE01 (1)	N02CC and encephalocele (OR 6.12, 95% CI 1.20-19.38) N02CC and pulmonary valve atresia (OR 5.25, 95% CI 1.04-16.48) N02CC05 and ASD (OR 11.99, 95% CI 1.6-89.73) N02CC06 and club foot/talipes equinovarus (OR 8.59, 95% CI 1.33-44.29)

More detail is provided than usual for p values due to the number of decimal places of relevance to the interpretation of the signal detection results.

‡Signal from original analysis not meeting revised FDR p-value threshold.

*Using validated data and adjusting for registry.

§Not validated in terms of CA or medication exposure and not adjusted for registry.

¥Adjusted for maternal age category.

$Laterality group includes atrial isomerism, dextrocardia, situs inversus, broncho-pulmonary isomerism, asplenia and polysplenia.

#Includes J05AX04, J05AB05, J05AB07, J05AB08, J05AB10, J05AF, J05AF01-12, J05AF30, J05AR01-09 and J05AR11-13 in adjusted analysis due to changes over time in the ATC coding of Ns/NtRTIs (including in combination).

Signal literature review

Of the 13 validated signals for which a literature review was conducted, previous evidence in the literature was found for 6 (Table 2).

Table 2 Results of literature review relating to 13 validated signals

Signal	Evidence to support signal	Medication uses and literature relating to their teratogenicity in humans
A02AD01 Ordinary salt combinations Cleft lip with or without cleft palate	C[£]	Ordinary salts are combinations and complexes of aluminium, calcium and magnesium compounds used as antacids. There is no evidence relating specifically to the teratogenicity of the ordinary salt combinations. One case-control study explores the teratogenicity of combinations and complexes of aluminium, calcium and magnesium. No increase in all CAs combined among those treated with aluminium magnesium hydrocarbonate (OR 1.5, 95% CI 0.3-8.9) or aluminium magnesium hydroxide (OR 0.6, 95% CI 0.2-2.4) was reported [39].

A03FA Propulsives (metoclopramide, cisapride, domperidone, bromopride, alizapride, clebopride and itopride) Total anomalous pulmonary venous return	C	Propulsives enhance gastrointestinal motility and are used to treat nausea and vomiting. Cohort studies have found no increase in the risk of all CAs combined [40–44], hypospadias or orofacial clefts [45] following exposure to the propulsives. There was no evidence of an association between transposition of the great vessels, ventricular septal defect (VSD), atrial septal defect (ASD), Tetralogy of Fallot, pulmonary valve stenosis or coarctation of the aorta [46] and first trimester exposure to metoclopramide (A03FA01). A retrospective cohort study found no significant association between first trimester exposure to metoclopramide and 'other anomalies of the circulatory system', a group which includes total anomalous pulmonary venous return [47]. However, the number of cases involved in this group was small and it is unclear what proportion, if any, had total anomalous pulmonary venous return. No studies have

		looked specifically at the risk of total anomalous pulmonary venous return.
A06AC Bulk-forming laxatives (ispaghula (psylla seeds), ethulose, sterculia, linseed, methylcellulose, triticum (wheat fibre), polycarbophil calcium, ispaghula combinations, sterculia combinations and linseed combinations) Anencephalus and similar anomalies	C[£]	Bulk-forming laxatives are used to treat constipation. The single cohort study exploring the teratogenciity of ispaghula (A06AC01) found no significant difference in the rate of all CAs combined between those who were exposed in the first trimester and those who were not [48].
A07DA Antipropulsives (diphenoxylate, opium, loperamide, difenoxin, loperamide oxide, morphine combinations and loperamide combinations)	B	Antipropulsives are used to treat diarrhoea. Two cohort studies explore the teratogenicity of loperamide (A07DA03) and found no increase in all CAs combined [49]. An association was found between loperamide exposure and hypospadias (RR 3.2, 95% CI 1.3– 6.6, n=7) but multiple

Syndactyly		comparisons mean that this may have been due to chance [50].
C02DB Hydrazinophthalazine derivatives (dihydralazine, hydralazine, endralazine, cadralazine) Atrial septal defect (ASD)	C[£]	Hydrazinophthalazine derivatives act on arteriolar smooth muscle and are used to treat hypertension. A single case-control study found no significant association between dihydralazine (C02DB01) exposure, before and throughout pregnancy, and all CAs combined [51].
G03AB03/G03AA07 Levonorgestrel and ethinylestradiol Gastroschisis	A	Levonorgestrel and ethinylestradiol is a combined oral contraceptive containing both an oestrogen and a progestogen. Evidence specifically relating to levonorgestrel and ethinylestradiol is limited to one large case-control study where 6/133 (4.5%) CA case and 8/129 (6.2%) non-malformed control infants were exposed to levonorgestrel and ethinylestradiol [52]. Exposure to oral contraceptives in early pregnancy does not increase the risk of all CAs

		combined [53,54], neural tube defects (NTD) [55–57], CHD [54] or orofacial cleft [58]. The evidence relating to gastroschisis is conflicting with some articles showing a significant association (68% of gastroschisis cases exposed vs. 26% of malformed controls [59]; aOR 1.8, 95% CI 1.3-2.7, n=40 [60]) and others showing none [61,62]. The same is true for genital anomalies [63–68]. One case-control study describes an increased risk of urinary tract anomalies following first trimester exposure to oral contraceptives [69].
G03DA Pregnen (4) derivatives (gestonorone, medroxyprogesterone, hydroxyprogesterone and progesterone) Complete absence of a limb	A	Pregnen (4) derivatives are progestogens, compounds with biological activity similar to progesterone, used in hormone replacement therapy, infertility and to treat menstrual problems. Cohort and case-control studies found no significant increase in all CAs combined with any of the pregnen (4) derivatives [70–76]. A cohort study found that

		medroxyprogesterone (G03DA02) increases the rate of CHDs, gastro-intestinal defects, CAs of the integument, chromosome defects and all other defects. These findings may be due to chance as multiple comparisons were made and the range of defects including chromosomal defects is not plausible [77]. A number of case-control studies have found a significant association between hypospadias and both hydroxyprogesterone (G03DA03) and progesterone (G03DA04) [78–80]. However, other studies have found no association [66,81,82] and recall bias is a concern [83]. In the 1960s and 70s a number of studies were published linking 'sex hormones' with an increased incidence of non-genital congenital malformations such as CHDs and limb reduction defects [84–90]. However, the evidence supporting the link between progestogens and contraceptive agents with non-genital malformations was contradictory,

		poor methodologically and the study material lacked uniformity [73,91,92]. By 1993 the controversy surrounding this issue meant that there had been 20 review articles written on this subject, none of which concluded that sex hormones produced non-genital organ teratogenesis [93,94].
G03DB Pregnadien derivatives (dydrogesterone, megestrol, medrogestone, nomegestrol, demegestone, chlormadinone, promegestone and dienogest) Hypospadias	A	Pregnadien derivatives are also progestogens and are used as per the pregnadien derivatives. A review of case-reports and 3 very small trials found no increase in all CAs combined with dydrogesterone (G03DB01) [95–98]. The broader medication group, the progestogens, have been associated with hypospadias [68,81,99] but these findings have not been consistent [66,79,83,100].
G03GB	A	Synthetic ovulation stimulants are used in infertility treatment. Across cohort and case-control studies there is no evidence that exposure to clomiphene citrate (G03GB02)

Synthetic ovulation stimulants (cyclofemil, clomifene and epimestrol) Hypospadias		in the periconceptional period increases the rate of all CAs combined. There is conflicting evidence of an association with NTDs [101–103]. Clomiphene has been associated with coarctation of the aorta [104,105], anencephaly, Dandy Walker malformation, septal heart defects, muscular ventricular septal defects, esophageal atresia, cloacal exstrophy, craniosynostosis and omphalocele but multiple comparisons and small numbers of cases make these findings tentative [105]. An association between periconceptional clomiphene exposure and the more severe, proximal forms of hypospadias [66,106–108], but not all forms of hypospadias combined [109,110], has been described.
L02AE	C[£]	Gonadotropin releasing hormone analogues are used in infertility treatment. Evidence relating to the teratogenicity of the GnRHa's is limited to case reports/series [111–114].

Gonadotropin releasing hormone analogues (GnRHa) (buserelin, leuprorelin, goserelin, triptorelin and histrelin) Laterality		There is no evidence for a pattern of anomalies but the numbers reported are small and there is potential for reporting bias.
J05AF Nucleoside and nucleotide reverse transcriptase inhibitors (Ns/NtRTIs) (zidovudine, didanosine, zalcitabine, stavudine, lamivudine, abacavir, tenofovir disoproxil, adefovir dipivoxil, emtricitabine, entecavir, telbivudine, clevudine) Congenital heart defects (CHD)	A	The Ns/NtRTIs are used to treat HIV/AIDS and chronic hepatitis. Case-control, cohort studies and a manufacturer maintained pregnancy registry explore the teratogenicity of individual Ns/NtRTIs and the group as a whole. There is no evidence that first trimester exposure to any of the individual Ns/NtRTIs, or the group as a whole, increases the rate of all CAs combined [115–119] First trimester exposure to zidovudine (J05AF01) has been found to increase the risk of CHD [119,120], but this has not been a consistent finding [121,122]. A significant association between first trimester exposure to ARV regimes containing at least one Ns/NtRTI
J05AF30	A	

Combinations of nucleoside and nucleotide reverse transcriptase inhibitors Pulmonary valve stenosis (PVS)		and CHD is reported [123]. There is no evidence relating to the risk of PVS as a specific CHD. Small numbers of cases have also suggested an increased risk of Central Nervous System (CNS) anomalies [122] and hypospadias [124] following first trimester exposure to zidovudine and head and neck defects following first trimester exposure to didanosine (J05AF02) [119].
N02CC Selective serotonin agonists (sumatriptan, naratriptan, rizatriptan, almotriptan, eletriptan and frovatriptan) Congenital constriction bands or amniotic bands	C	Selective serotonin agonists, also called triptans, are used to treat migraines. Cohort studies and a manufacturer maintained pregnancy registry explore the teratogenicity of these medications, sumatriptan (N02CC01) in particular. First trimester exposure to sumatriptan does not significantly increase the rate of all CAs combined [125–130]. Eletriptan (N02CC06) was found to significantly increase the rate of all CAs combined but this was based on 14 exposures and may

		have been a chance finding [131]. None of the other triptans [128,130,132], or the triptans as a group appear to increase the rate of all CAs combined [128,133,134].

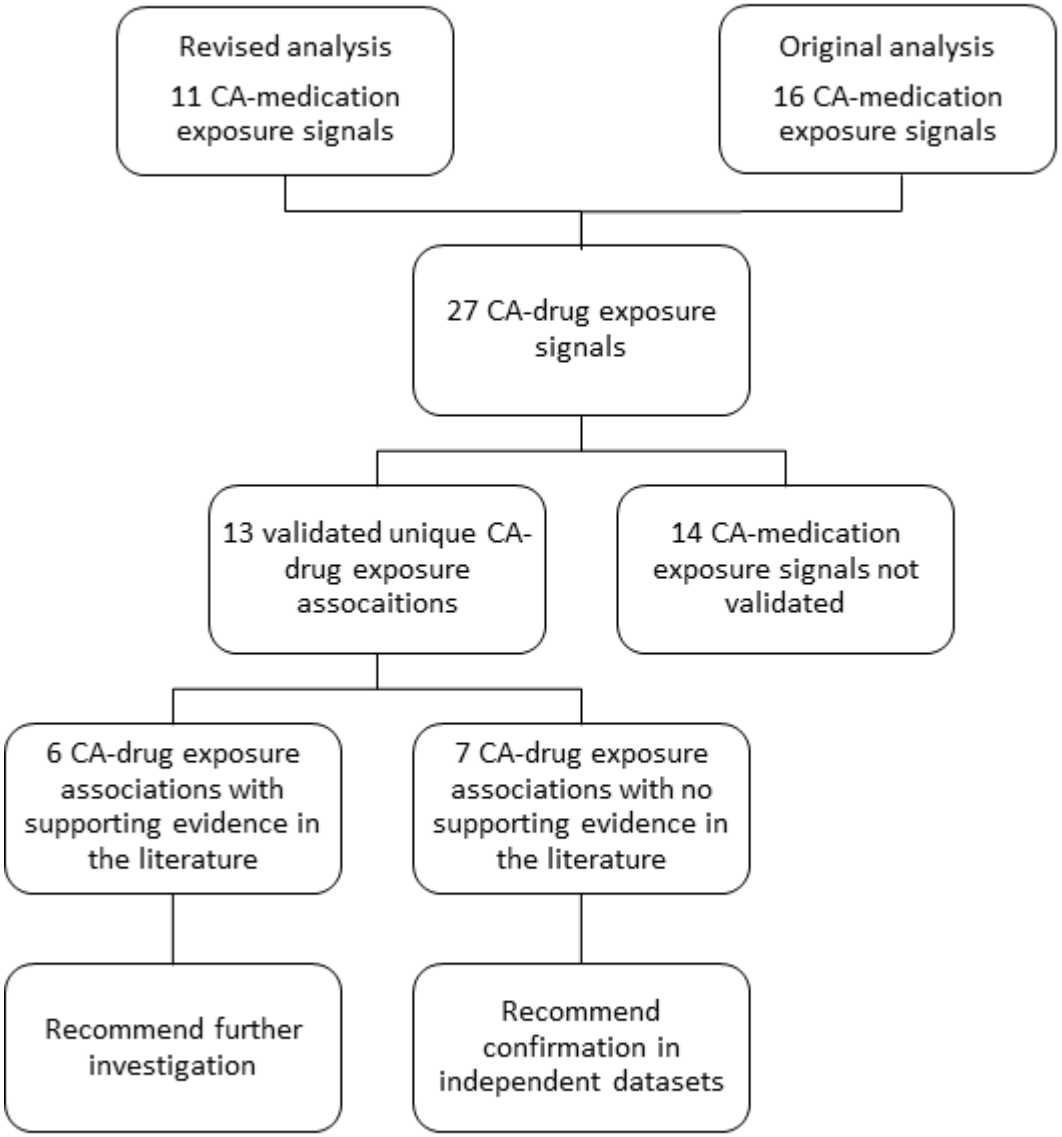
A teratogenicity leading to signal CA described in literature

B teratogenicity leading to other CA described in literature

C no evidence of teratogenicity

£ published evidence minimal

Figure 1 Signal evaluation flow diagram



Discussion

We have found 13 CA-medication exposure signals which require further confirmation. There was evidence in the literature, albeit conflicting at times, to support 6 of the 13 signals [59–62,66,68,79,81,83–90,93,94,99,100,106–110].

These 6 signals have been strengthened and should be prioritised for further evaluation. Four of these signals were related to sex hormones (gastroschisis and the contraceptive levonorgestrel/ethinylestradiol; complete absence of a limb and pregnen (4) derivatives; hypospadias and pregnadien derivatives; hypospadias and synthetic ovulation stimulants). We also had as yet unvalidated data that some other anomalies might be associated with these medications. Sex hormone-based medications accounted for 24.8% of the medication exposures in the database [Ref. attached article]. The other two of these signals were congenital heart defects and pulmonary valve stenosis associated with nucleoside/nucleotide reverse transcriptase inhibitors, antivirals used for HIV and chronic hepatitis. For all of these signals, the possibility of confounding by indication, or by co-exposures, should be considered. The progestogens are used to 'support' pregnancies at risk of early loss. It may be that this leads to increasing survival of CA affected foetuses [135]. Sub-fertile women have been found to have a higher risk of having a child with a CA regardless of whether or not they receive infertility treatment [105,136–138], and this or other co-exposures may confound the interpretation of medication use related to sub-fertility or infertility [138]. Those receiving antiviral treatment for HIV or Hepatitis infection, may have other exposures leading to an increased risk of CAs [139]. However, the case-malformed control approach used in this study will have negated this issue to some extent as the comparison group also have CA.

The only evidence that the antipropulsive antidiarrheals may be teratogenic was a single report of an association with hypospadias [50], rather than syndactyly as in our results. These two anomalies are usually considered aetiologically unrelated.

The remaining six statistical signals did not have supporting evidence in the literature and should be confirmed in an independent dataset. For selective serotonin

agonists a number of previous studies have found no association with CA [125–134] but these were too small to find an anomaly as rare as congenital constriction bands. Hydrazinophthalazine derivatives, anti-hypertensives which act on arteriolar smooth muscle, have one small previous negative study [51]. Other types of antihypertensives, such as ace inhibitors, have been associated with an increased risk of CA [140] but the underlying maternal hypertension also appears to play a role in the development of CA [141] . While there are concerns about assisted reproduction in general in relation to CA risk [142], and two of our other signals discussed above are medications used in assisted reproduction, there is only minimal case report evidence [111–114] relating to gonadotropin releasing hormone analogues, and none of these case reports relate to laterality anomalies. Previous studies of the propulsives [40–47] have been negative regarding teratogenicity and there is no evidence to support our finding. The ordinary salts and bulk-forming laxatives are generally assumed to be safe, have low bioavailablity, do not interefere with normal physiologic salt balance and therefore not specifically studied.

The signal detection methodology used in EUROmediCAT was based on a 50% FDR. This means that half of the associations found are expected to be chance associations i.e. not causal. Due to this uncertainty, and the difficulties of interpretation discussed above, medication decisions should not be made based on the CA-medication exposure signals identified but further research should be conducted.

Strengths and Limitations

A strength of this study is the use of the EUROmediCAT central database. EUROmediCAT's international population based database contains detailed coding of all CAs [28] and includes TOPFA cases which constitute a large proportion of some CA [143]. The diagnosis of CAs is standardised across the registries involved and will have ensured consistency in the diagnosis [26]. There will also be much less under-reporting and bias than in spontaneous reporting pharmacovigilance systems as all major CAs are recorded in EUROCAT, not just those which clinicians consider to be important enough or potentially linked to a medication exposure. While the EUROmediCAT database contains detailed information on medications taken during the first trimester of pregnancy there is known under ascertainment of some medications [29,144] but while this may reduce the sensitivity of the system to detect certain teratogenic medications, it should not lead to bias due to the use of malformed controls.

It was only possible to validate the data relating to the exposed cases. This means that while the number of exposed cases may have decreased, due to errors found in data coding, the number of exposed controls will not have changed. As a result the data validation process could only decrease the ORs. We found evidence that other anomalies were also associated with the signal medications, but at lower levels of statistical significance which did not surpass the FDR threshold, and did not validate these data. However, data validation for the main findings is a strength of this study.

The signal detection process used did not take prior literature into account during the statistical analysis [145] but instead brought this in at the signal evaluation stage. In the EUROmediCAT analyses of antiepileptics, antidiabetics, antidepressants and

antiasthmatics [20–23], we first searched the literature before evaluating existing signals and detecting new signals. The signal detection process we report in this paper is intended to be used in addition to the drug class by drug class approach. It can be used to identify the most highly significant associations in the database for drug classes not otherwise undergoing analysis. We recognise that there may be many other associations in the data that did not meet the FDR threshold but which are nevertheless of potential interest. Indeed, this is as shown by our evaluation of the 16 signals arising from the original signal detection analysis which included a number of associations reported previously in the literature.

While the literature search was extensive it is possible that relevant articles may have been missed, particularly negative evidence for a medication exposure when analysed as one of many aetiological factors in a case-control study. We were assessing whether previous literature existed but did not conduct a meta-analysis of the evidence to date, and this may lead to highlighting positive over negative evidence, although all evidence found is presented. It was necessary to search for each of the individual medications, rather than the broader medication group as the 4th ATC level, chemical subgroup, was not always used in the literature or databases and returned little or no information for some of the signals. Without prior hypotheses about the mechanism of action, it can also be difficult to decide how broadly to look for related literature – for example there is a large literature on sex hormones as a class, but much less related to specific sex hormones. While positive evidence in the literature regarding risk of all CAs combined could be considered supportive, negative evidence is more difficult to interpret, since few medications increase the rate of all CAs combined, instead tending to increase the rate of specific CAs [146].

As far as possible changes, over time, in the ATC codes used for particular medications were taken into account in both the signal detection analysis and the signal evaluation. It is possible however that some changes were missed, potentially leading to signals being missed as the exposed cases would be split across more than one ATC code in the dataset.

Although all the cases were confirmed as first trimester exposures it is not known if these exposures actually occurred during the critical period for CA development [8]. Similarly there was no information available in terms of the doses of medications taken for the majority of cases. If it was possible to identify a dose response relationship or show exposure during the critical period for development of the specific CAs this would provide support for a causal relationship [146]. Our protocol did not include assessment of biological plausibility or possible teratogenic mechanisms [147]. Although grouping of CA or of medications by potential teratogenic mechanism has been advocated [3], we found this to be of limited use since the same CA are often related to a number of potential mechanisms, and the current imperfect knowledge of mechanisms is one of the drivers of signal detection in postmarketing surveillance.

Conclusion

A statistical signal detection analysis was conducted using the EUROmediCAT central database. Six signals had some prior supporting evidence and these should be prioritised for further investigation before being evaluated in relation to clinical decision making. A further seven CA-medication exposure signals were found which had no prior supporting evidence and these need to be confirmed in independent datasets.

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Supplementary Table 1: EUROmediCAT signal detection dataset

EUROCAT Registry	Birth years enrolled	Exposed Foetuses with Congenital anomalies (n)	Foetuses with Congenital anomalies following data cleaning by timing of exposure[a] (n)	Data loss by data cleaning (%)	Total eligible ATC-coded exposures (n)	Average *number* of ATC-coded medication exposures per pregnancy
Belgium, Antwerp	1997-2011	358	354	1	529	1.49
Croatia, Zagreb	1995-2010	184	180	2	228	1.27
Denmark, Odense	1995-2011	234	234	0	357	1.53
France, Paris	2001-2011	659	659	0	968	1.47
Germany, Mainz	2005-2011	142	139	2	158	1.14
Ireland, Cork & Kerry	1996-2009	259	258	0	355	1.38

Italy, Emilia Romagna[b, c]	1995-2011	2,322	2,322	0	3,826	1.65
Italy, Tuscany	1995-2011	1,082	1,043	4	1,418	1.36
Malta	1996-2011	298	297	0	445	1.50
Netherlands, North Netherlands	1995-2011	2,374	1,844	22	3,036	1.65
Norway	2005-2010	3,052	3,052	0	5,537	1.81
Poland (excl. Wielkopolska)	1999-2010	11,997	1,958	84	2,450	1.25
Poland, Wielkopolska	1999-2010	2,713	409	85	552	1.35
Switzerland, Vaud	1997-2011	298	294	1	435	1.48
UK, Wales	1998-2011	1,907	1,907	0	2,807	1.47
Total	1995-2011	27,879	14,950	46	23,101	1.55

[a] Exclusion of CA registrations with only medication exposures of unknown timing

[b] During the period 1995 to 2004 Emilia Romagna database had space for only 5 medications to be recorded.

[c] Terminations of pregnancy for fetal anomalies were excluded from the Emilia Romagna registry as information on medications is only available for live and still births

Supplementary document 1: Literature review methodology

Databases

REPROTOX (http://reprotox.org)

This database is extensive and covers a wide range of exposures including medications, vaccines, illicit substances and chemicals. Information is provided with an initial summary followed by a review of the literature. This review covers evidence of teratogenicity in animals and humans, potential effects of the chemical on the pregnancy (for e.g. delaying/stimulating delivery) or neonate (for e.g. respiratory depression after delivery or neurological side effects in later life) and information relating to breast feeding. This review is well referenced and frequently updated (usually within the previous month or two). Caution should be used when a drug group, rather than a specific drug, is being reviewed. As per the issues highlighted below, in terms of the difficulties in finding appropriate information relating to the 4th ATC level, a review of a drug group can miss important associations in the literature. For example (at the time of conducting the literature review for this article) the summary relating to Selective Serotonin Reuptake Inhibitors (SSRIs) did not include a paper from the New England Medical Journal - 'Use of Selective Serotonin-Reuptake Inhibitors in Pregnancy and the Risk of Birth Defects'. This article was included in the REPROTOX reviews relating to specific SSRIs but not in the review relating to the drug group. This highlights the methodological difficulties in summarising the evidence at a drug group (3rd or 4th ATC level) compared to an individual drug level (5th ATC level).

TOXBASE (http://www.toxbase.org)

This database is produced by the UK Teratology Information Service. While it covers chemical exposure, self-poisoning (deliberate or accidental) and snake bites etc. it also has a section specifically for exposures which occur during pregnancy. This section covers a wide range of drug or chemical exposures as well as a number of maternal health conditions. Unlike REPROTOX this database is restricted to drugs prescribed in the UK. The information provided starts off with the summary information which is available on the UKTIS website. The document then details: preclinical (animal) data, human data (congenital malformations, neonatal effects, overdose in pregnancy, NICE guideline recommendations and paternal exposure) and the outcome of any exposure cases reported to NTIS (prospectively and retrospectively). References to the literature are provided in this document but these documents may not have been updated for a while.

DART (Developmental and Reproductive Toxicology)
http://toxnet.nlm.nih.gov/newtoxnet/dart.htm

DART (one of the TOXNET databases) provides more than 200,000 journals references covering teratology and other aspects of developmental and reproductive toxicology. It has references from the early 1900s to the present. New references are added weekly. The vast majority of references returned are relevant to teratogenicity.

PubMed (http://www.ncbi.nlm.nih.gov/pubmed/)

PubMed comprises more than 25 million citations for biomedical literature from MEDLINE, life science journals, and online books. PubMed citations and abstracts include the fields of biomedicine and health, covering portions of the life sciences, behavioural sciences, chemical sciences, and bioengineering. As this database is not limited to references relating to teratology it is necessary to include additional search terms to identify relevant literature.

ATC classification

There are 5 levels in the ATC classification. The complete classification of metformin below illustrates the structure of the code:

- A Alimentary tract and metabolism
- (1st level, anatomical main group)

- A10 Drugs used in diabetes
- (2nd level, therapeutic subgroup)

- A10B Blood glucose lowering drugs, excl. insulins
- (3rd level, pharmacological subgroup)

- A10BA Biguanides
- (4th level, chemical subgroup)

- A10BA02 metformin
- (5th level, chemical substance) [1].

There is often nothing available in the literature specifically relating to the teratogenicity of drugs at a 4th level (e.g. biguanides). However when searching at the 3rd ATC level (e.g. blood glucose lowering drugs excluding insulins) it was almost impossible to pull out information relating specifically to the 4th group level. You also miss a lot of relevant literature doing this and importantly the WHO states that: 'Substances classified in the same ATC 4th level (4ths) cannot be considered pharmacotherapeutically equivalent since their modes of action, therapeutic effects, drug interactions and adverse drug reaction profiles may differ' [1]. In an attempt to identify as much relevant literature as possible relating to a 4th level signal it was therefore necessary to also search for each drug at the 5th level which contributed to the 4th level group.

Search process

1. TOXBASE and REPROTOX

Used to get a summary re: teratogenicity and to identify the main articles. Searched using the chemical substance and subgroup names (5th and 4th ATC levels), as shown in table 1 below.

2. DART and PubMed

Used to identify any older, more recent or obscure articles which were not included in the TOXBASE or REPROTOX summaries. Searched using terms to represent the chemical substance and subgroup names (5th and 4th ATC levels), as shown in table 1 below. Additional search terms were included in order to restrict the search results to literature relevant to potential drug teratogenicity i.e. 'terat*', 'congen*', 'malf*' and ''anom*'.

3. Reference list of identified articles

Used to identify any older or obscure articles which were not previously identified.

Table 1 Signal search terms

Signal drug/group	4th ATC level	DART and PubMed 4th ATC level search terms	5th ATC level	DART and PubMed 5th ATC level search terms
A02AD01 Ordinary salt combinations	Combinations and complexes of aluminium, calcium and magnesium compounds	• (aluminium AND compound*) • (calcium AND compound*) • (magnesium AND compound*)	• Ordinary salt combinations • Magaldrate • Almagate • Hydrotalcite • Almasilate	• (ordinary AND salt) • magaldrate • almagate • hydrotalcite • almasilate
A03FA Propulsives	Propulsives	• propulsive*	• Metoclopramide • Cisapride • Domperidone • Bromopride • Alizapride • Clebopride • Itopride	• metoclopramide • cisapride • domperidone • bromopride • alizapride • clebopride • itopride
A06AC Bulk-forming laxatives	Bulk-forming laxatives	• (bulk AND laxative*)	• Ispaghula (psylla seeds) • Ethulose • Sterculia	• ispaghula • psylla • ethulose • sterculia

			• Linseed • Methylcellulose • Triticum (wheat fibre) • Polycarbophil calcium • Ispaghula combinations • Sterculia combinations • Linseed combinations	• linseed • methylcellulose • triticum • (wheat AND fibre) • polycarbophil
A07DA Antipropulsives	Antipropulsives	• antipropulsive*	• Diphenoxylate • Opium • Loperamide • Difenoxin • Loperamide oxide • Morphine combinations • Loperamide combinations	• diphenoxylate • opium • loperamide • difenoxin • (morphine AND combination*)

C02DB Hydrazinophthalazine derivatives	Hydrazinophthalazine derivatives	• hydrazinophthalazine	• Dihydralazine • Hydralazine • Endralazine • Cadralazine	• dihydralazine • hydralazine • endralazine • cadralazine
G03AB03/G03AA07 Levonorgestrel and ethinylestradiol	• Progestogens and estrogens, sequential preparations • Progestogens and estrogens, fixed combinations	• progestogen* • estrogen* • oestrogen*	• Quingestanol and ethinylestradiol • Lynestrenol and ethinylestradiol • Megestrol and ethinylestradiol • Norethisterone and ethinylestradiol • Norgestrel and ethinylestradiol	• quingestanol • lynestrenol • Megestrol • norethisterone • norgestrel • levonorgestrel • medroxyprogesterone • desogestrel • gestodene • norgestimate • drospirenone • norelgestromin • nomegestrol • chlormadinone • dienogest

			• Levonorgestrel and ethinylestradiol • Medroxyprogesterone and ethinylestradiol • Desogestrel and ethinylestradiol • Gestodene and ethinylestradiol • Norgestimate and ethinylestradiol • Drospirenone and ethinylestradiol	• ethinylestradiol • estradiol

			• Norelgestromin and ethinylestradiol • Nomegestrol and estradiol • Chlormadinone and ethinylestradiol • Dienogest and ethinylestradiol	
G03DA Pregnen (4) derivatives	Pregnen (4) derivatives	• pregnen	• Gestonorone • Medroxyprogesterone • Hydroxyprogesterone • Progesterone	• gestonorone • medroxyprogesterone • hydroxyprogesterone • progesterone
G03DB Pregnadien derivatives	Pregnadien derivatives	• pregnadien	• Dydrogestero ne • Megestrol • Medrogeston e	• dydrogestero ne • megestrol • medrogeston e

			• Nomegestrol • Demegestone • Chlormadinone • Promegestone • Dienogest	• nomegestrol • demegestone • chlormadinone • promegestone • dienogest
G03GB Synthetic ovulation stimulants	Synthetic ovulation stimulants	• (synthetic AND ovulat*) • (ovulat* AND stimul*)	• Cyclofemil • Clomifene • Epimestrol	• cyclofemil • clomifene • epimestrol
L02AE Gonadotropin releasing hormone analogues (GnRHa)	Gonadotropin releasing hormone analogues (GnRHa)	• gonadotropin • GnRHa • gnrha • GnRH • gnrh	• Buserelin • Leuprorelin • Gosorelin • Triptorelin • Histrelin	• buserelin • leuprorelin • gosorelin • triptorelin • histrelin
J05AF Nucleoside and nucleotide reverse transcriptase inhibitors (Ns/NtRTIs)	Nucleoside and nucleotide reverse transcriptase inhibitors (Ns/NtRTIs)	• nucleoside • nucleotide • (nucleoside AND nucleotide) • Ns/NtRTI*	• Zidovudine • Didanosine • Zalcitabine • Stavudine • Lamivudine • Abacavir	• zidovudine • didanosine • zalcitabine • stavudine • lamivudine • abacavir

J05AF30 Combinations of nucleoside and nucleotide reverse transcriptase inhibitors		• ns/ntrti*	• Tenofovir disoproxil • Adefovir dipivoxil • Emtricitabine • Entecavir • Telbivudine • Clevudine	• tenofovir • adefovir • emtricitabine • entecavir • telbivudine • clevudine
N02CC Selective serotonin (5HT1) agonists	Selective serotonin (5HT1) agonists	• (selective AND serotonin) • (serotonin AND agonist*) • triptan* • 5HT1 • 5ht1	• Sumatriptan • Naratriptan • Rizatriptan • Almotriptan • Eletriptan • Frovatriptan	• sumatriptan • naratriptan • rizatriptan • almotriptan • eletriptan • frovatriptan

Reference

1. WHO Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC classification and DDD assignment. Oslo: WHO Collaborating Centre for Drug Statistics Methodology; 2014.