Assessment of historical evidence on Primodos and congenital malformations – a synopsis

Background

In January 2014 Dan Poulter met with Yasmin Quereshi MP to discuss the alleged association between use of Primodos, a hormone pregnancy test (HPT), and the occurrence of congenital anomalies in the offspring. The meeting agreed that an assessment of all relevant historical evidence was needed.

As a result, the Medicines and Healthcare products Regulatory Agency (MHRA) has reviewed the key evidence on the possible effects of HPTs such as Primodos, taken by the mother during pregnancy, on the subsequent development of the child. The findings of the review (annex 1) are summarised below.

Evidence reviewed

The review included 36 studies and other related data including an episode of The London Programme that was never screened but which presented the available evidence up to 1978 and a number of published reviews. These tried to establish whether or not HPTs were capable of causing the abnormalities that had been observed in studies.

The first study to identify a possible association between HPTs and congenital abnormalities was conducted by Dr Isobel Gal in 1967. This study observed that more mothers of children with spina bifida had used a HPT than the same number of mothers of healthy babies. This finding triggered a number of further studies over the following 30 years by many different investigators. These investigated not only a possible effect of HPTs on the development of spina bifida and other related conditions affecting the nervous system (neurological conditions) but also on the development of cleft lip and palate, heart defects, abnormal formation of the arms or legs (limb reduction defects), oesophageal defects, and a syndrome affecting many different organs (VACTERL).

Findings

The studies are inconsistent in their findings for an association between use of HPTs and congenital anomalies and are not considered sufficient to conclude that an association exists.

The main concern stems from the fact that the majority of the evidence is from studies and case reports which have important limitations. Because the studies were largely conducted 20-40 years ago the techniques used are relatively unsophisticated by today's standards.

Studies looking specifically at the effects of medicines in pregnancy are subject to unique challenges. In particular they mainly look back at events that have happened in the past and so there are difficulties in determining accurately what medicines a mother may have taken and at what stage of her pregnancy. In addition it is not known whether mothers who took medicines in pregnancy were different in other ways which may have affected the outcome of their pregnancies from mothers who did not.

A number of the published reviews comment on the poor quality of the data collected in most of the studies and the lack of data from robust prospective studies.

Most concluded that the evidence does <u>not</u> support a causal association between exposure to HPTs during early pregnancy and developmental malformations but acknowledged that the evidence is insufficient to definitively rule out such an association. A minority concluded that there may be some evidence for a small increase in cardiac defects but firm conclusions are not possible.

Conclusion

The body of evidence for an association between HPTs and congenital anomalies is mixed, with some studies finding a strong association, some finding a weak association and many others finding no association.

Although it is understandable to suspect that there may be an association between a medicine and a condition that develops after taking it, particularly when that medicine is taken during pregnancy, this may not necessarily be the case. The timing of exposure is critical and needs to occur during the period of gestation when the fetus is susceptible to the observed outcome. The association also needs to be plausible; in this case the observation of isolated but different anomalies in different studies is particularly difficult to interpret. If HPTs really were teratogenic, all studies should have observed increased numbers of all the observed that have been anomalies because women were exposed to HPTs at random times throughout gestation. In addition the scientific methodology needs to be sufficiently robust as to exclude false positive findings ie the possibility that other factors could have been responsible for the observed finding - this is not the case for the vast majority of studies.

Having carefully considered the available published evidence, our position therefore remains that the data are not sufficient to conclude that there is a causal association between the use of Primodos (or any HPT) and congenital abnormalities.

Medicines and Healthcare Products Regulatory Agency, March 2014

ANNEX 1

Assessment of historical evidence on Primodos and congenital malformations

Background

Awareness of a possible teratogenic effect of exogenous female sex hormones in early pregnancy was heightened following the identification of an association between diethylstilboestrol and clear-cell adenocarcinoma in the female offspring, and a virilising effect of progestogens on the female fetus.

A study by Gal in 1967 was the first to identify an association between sex hormones used as hormone pregnancy tests (HPT) and congenital anomalies, in this case neural tube defects. This observation stimulated a great deal of further research over the course of the next two decades, the results of which are conflicting.

In response to growing concern that HPTs, and Primodos in particular, were responsible for a number of congenital malformations, we have carried out a detailed assessment of the key data (focusing on possible effects other than the known virilising effect on female fetuses).

Evidence

We have assessed 36 observational (non-interventional) studies that evaluated the use of HPTs in pregnancy. In addition, we have reviewed a number of supporting letters, abstracts, surveys, ecological studies, case reports, case series, study re-analyses, pre-clinical studies and reviews of the published literature. The earliest study was that by Smithells in 1964 and the most recent by Tümmler in 2013; however the majority of the data were published between 1972 and 1985 (see table in Appendix 1).

As may be expected from studies conducted so long ago, the design and methodological rigour of many is poor. In many, neither the type of hormone evaluated nor its indication for use are clearly specified, with studies very often pooling data from women taking hormones for bleeding during pregnancy, pregnancy diagnosis, threatened miscarriage, menstrual irregularities or contraception.

The main limitations common to many of the studies relate to:

- *Method of selection of controls/ lack of controls* – use of normal babies as controls increases the likelihood of recall bias; the selection of historical controls or controls from a different region/hospital potentially resulting in prescribing bias; use of comparators with a different susceptibility to the outcome

- *Reliability of information* – accuracy of estimated gestational age at exposure; accuracy of information recorded in medical notes/remembered by women; recall bias in retrospective studies due to the increased pressure on mothers of malformed babies to remember what medicines they took during pregnancy; lack of blinding in ascertainment of exposure and outcome

- *Role of confounding factors* – unidentified/unrecorded/unverified potentially important confounding factors and lack of correct for them; incomplete or no matching of cases and controls; susceptibility/indication/protopathic bias due to inherently different risk in women exposed/unexposed to HPTs

- *Categorisation of exposure*– inadequate analysis or interpretation of data according to pharmacologically different hormones/doses/durations/ indications; lack of unbiased method of ascertainment of exposure

- *Relevance of stage of pregnancy at the time of HPT* – insufficient consideration of biological plausibility of exposure time; time of exposure during gestation often too broad for the types of malformations reported

- *Type of malformation* – inconsistency in definition between studies; requirement for unbiased method of ascertainment of anomalies; inconsistency in type of defect identified in different studies

- *Statistical robustness* - small numbers of cases exposed to HPTs; lack of correction for multiple comparisons

- *Background incidence* – relatively high natural incidence of many malformations

Although many of the later studies did attempt to address at least some of these concerns many are still considered to suffer from some form of bias.

Epidemiological evidence
The data are conflicting with respect to exogenous female sex hormones and congenital anomalies. Nevertheless a substantial body of evidence exists in support of an association. The anomalies most commonly identified include neural tube defects (NTD), cleft lip and palate, limb reduction defects, general cardiovascular defects, transposition of the great vessels (TGV), conotruncal malformations, oesophageal atresia, and VACTERL. The evidence for each is examined in more detail below and in the table in appendix 1.

Neural tube defects
Gal et al (1967, 1972) reported a significant association between Primodos and spina bifida in a case-control study in which cases and controls were matched on various factors - but not folic acid or alcohol, which are now known to be significant risk factors. This association was refuted by Laurence et al (1971) who, in a larger study, found no significant difference between cases (8.1%) and controls (6.8%) exposed to HPTs. The main criticisms of Gal's findings included the appropriateness of case and control selection (Laurence 1972) and timing of exposure; it was observed that a large proportion of cases must have been exposed after the critical period of organogenesis (Sever 1973).

A study by Oakley et al (1973) with negative findings included sufficiently large number of NTD cases to be statistically reliable; however there was no control group and many risk factors were not accounted for. Results of a relatively well-designed case-control study conducted by Greenberg et al (1977) were consistent with a general teratogenic effect but there was no suggestion of a specific effect on the neural tubes.

Limb reduction defects
A significant association between exposure to exogenous sex hormones during gestation and limb deficiencies only was reported in male offspring only by Janerich et al (1974), but included only 3 cases specifically exposed to HPTs. Criticisms of this study included the exposure of 2 cases in the first month of gestation when the risk of limb reduction defects is low. In addition, cases with both unilateral and bilateral deformities were included and unilateral limb reduction defects are thought more likely due to vascular disruption or genetic anomalies (Wilson 1981). Hellstrom et al (1976) reported 7 cases exposed to exogenous hormones (3 HPT) compared with 1 control (mothers of children with spina bifida), however their study was limited by memory bias and small sample size.

Although Oakley et al (1973) observed a similar proportion of HPT use in a study that included all defects (15% for limb reduction deformities) he concluded that this may mean that HPTs are not associated with malformations or they cause an increase in all defects which is unlikely on biological grounds. This study included no control group and many risk factors were not accounted for. Jaffe et al (1975) observed a high incidence of limb reduction abnormalities of 1 per 1000 babies born in a single hospital; however, there was no control group and only 2 mothers were exposed to sex hormones, in both cases outside of the critical period for limb reduction defects.

The case-control study by Greenberg et al (1977) included 4 groups of visible or severe malformations, including limb malformations (n=59) of which 6 mothers had been exposed to a HPT. These authors concluded that their data did not support an association between HPTs and a specific malformation but did support a general teratogenic effect, the size of which was not great. By contrast a significant association was observed between exposure to HPTs and limb defects (OR 2.16, 95% CI 1.24, 3.76) in a case-control study by Lammer (1986). However, the large number of statistical tests carried out in this study mean that the association could have been due to chance.

VACTERL
Nora and Nora (1973) reported a significantly higher exposure in mothers of babies with at least 3 major anomalies of VACTERL syndrome to any estrogen/progestogen oral contraception or HPT compared with controls (9% in cases vs 1.5% in controls, p<0.001). No information on matching of cases and controls was provided and there was a lack of information on confounders that were considered. The same authors described another case-control study (Nora and Nora 1975) in which 15 cases were matched with patients with chromosomal abnormalities and an additional 30 controls with murmurs or benign cardiac findings. Significant differences were again observed between cases and controls, with a higher proportion of cases being exposed to hormones and HPTs. However, the authors state that women were subject to "considerable probing" if the initial answers were negative regarding hormone intake. In addition confirmatory data on exposure was not found in more than half of charts, hormones were stated to have been taken for "a variety of reasons" and, while 24 (7.6%) of those who had taken estrogen/progestogen at some time during pregnancy, only 10 were exposed during the critical period of organogenesis (3.1%).

Another case-control study by Nora and Nora (1978) found a relative risk of 8.4 when comparing the exposure of cases with VACTERL and controls to exogenous progesterone and oestrogen (43% of cases vs. 8% of controls, p<0.001). As with

their other studies, limitations included the timing of exposure, lack of adjusting for confounding factors and no information on indication for hormone use.

Goujard et al (1977) did not encounter any cases of VACTERL in a prospective survey of 12,764 women that identified 216 cases of "unequivocal malformations", and found no difference between exposed and unexposed women with respect to other major abnormalities.

Congenital heart defects
Levy et al (1973) suggested that hormonal treatment might be one predisposing factor in the multifactorial causation of congenital heart disease, based on the identification of a significant increase in TGV in babies of exposed women. However, of the 7 exposed cases 3 mothers had other pre-disposing factors, including diabetes, and only 1 received a HPT. Nishimura et al (1974) examined over 450 induced abortuses alive in utero and found no cases of TGV exposed to progestogens and/or estrogens but a lack of information is available regarding other factors. A case-control study conducted by Mulvihill et al (1974) reported no difference in exposure to progestogens between cases with TGV and controls with normal hearts or ventricular septal defects but methodological details are too sparse to draw any conclusion about validity of results.

A large prospective study by Heinonen et al (1977) reported an adjusted RR of 2.1 for exposure to oestrogen/progesterone and cardiovascular defects, though four of the cases were exposed in the 1st lunar month before the critical period, and 3 cases were exposed in the 4th lunar month when embryogenesis of the cardiac structures is complete (Wilson 1981). The base data contributing to this study was subsequently re-examined in detail with the conclusion that the findings did not support an association between exposure to sex hormones and serious CHD (Wlison 1984).

In three studies (2 case-control and 1 cohort) Nora and Nora (1978) found significant associations between exposure to oestrogen/ progesterone and congenital heart defects, with relative risks ranging from 3.55 to 6. However, little information on the nature of the hormones or the gestational age at exposure was provided and 2 of the 6 cases of congenital heart defect (CHD) involved only patent ductus arteriosus, which is not considered a malformation but a result of postnatal pathophysiology.

The hypothesis that sex hormone exposure during pregnancy can cause CHD is supported by the results from a case-control study by Janerich et al (1977) in which a RR of 7.5 was estimated after controlling for family history. The number of exposed cases was relatively small (n=18 of which 10 HPTs) and though cases and controls were matched on some factors, controls were normal babies therefore introducing the possibility of recall bias. Despite the high RR estimate Janerich estimated no more than 19 additional cases of CHD would be expected among 100,000 births if the observed association was causal. In a prospective survey focussing on major abnormalities, including CHD, no difference was observed in rates of CHD between exposed mothers (4.29 per 1000) and unexposed mothers (4.07 per 1000) (Goujard et al, 1977). This survey avoided recall bias due to it being prospective but there is no information on risk factors of the women at baseline.

A small but non-significant association between HPTs and all CHD (prevalence ratio estimate 1.3, 90% CI 0.8-2.2) was found in a study by Rothman et al (1979). While a stronger association was observed for total anomalous pulmonary venous return (prevalence ratio estimate 11, 90% CI 1.9-45) this was based on just 2 cases. Rothman concluded that if exogenous hormones do cause an increase it is only a modest one.

In a study that included 3 groups of controls (matched on various factors) Ferencz et al (1979) failed to show an association between HPTs and conotruncal cardiac malformation (3.6% in cases vs. 5.1%, 7.6% and 3.4% in the 3 groups of control groups). The timing of exposure during pregnancy was not presented.

Oesophageal atresia
In an uncontrolled study Oakley et al (1973) noted a high frequency of HPT use in mothers of babies with oesophageal atresia (27.3%) compared with other congenital malformations and suggested further study regarding this malformation. An ecological case study which looked at 345 cases of atresia did not support the suggestion that oral contraceptives or oral HPTs cause oesophageal atresia alone or as part of VACTERL (David et al 1974). However, details on the methodology are sparse and the study suffers from the usual limitations of ecological assessments. Lammer et al (1986) reported a significant association between HPTs and oesophageal atresia in a case-control study; however, this was based on only 6 exposed cases.

Cleft lip or palate
No difference in the proportion of patients with cleft lip or cleft palate was observed among the children of 433 women exposed to HPTs (11.3% and 13.2% respectively) in an uncontrolled retrospective study (Oakley et al, 1973). A retrospective case study by Brogan et al (1975) found that 10% of 222 cases with cleft lip and palate had received oral or parenteral HPTs between the 5th and 8th weeks of gestation. Although no conclusions can be made as there was no control group, the authors suggested that if hormones produce such deformities it is at a low rate and probably in women already pre-disposed.

In Greenberg's case-control study (1977) oral clefts were one of the four major malformations specifically evaluated (412 cases, of which 6 mothers had been exposed to a HPT). The study adjusted for several confounding factors and observed a significant association between cases with any of the 4 malformations and exposure to HPTs, even after excluding women with a history of malformations (ratio case: control – 1.9, p<0.01).

General teratogenicity
A number of studies have evaluated the effect of exogenous sex hormones on malformations in general (Spira, 1972; Oakley, 1973; Haller, 1974; Nishimura, 1974; Harlap, 1975; Kullander 1976; Goujard, 1977; Torfs, 1981; Michaelis 1983; Katz, 1985; Resseguie, 1985; Martinez-Frias, 1998; Hemminki, 1999). Two studies, a prospective record linkage study in 11,500 babies (Harlap, 1975) and a retrospective cohort study in Finland (Hemminki, 1999), found evidence for an association. Eleven studies found no evidence for an association including: a prospective cohort study in 20,000 French women (Spira, 1972); a retrospective survey of 433 babies with major malformations (Oakley, 1973); a prospective cohort study in 3,588 German women (Haller, 1974); an examination of more than 5,600 aborted fetuses (Nishimura,

1974); a prospective study of 6,476 pregnancies in Sweden (Kullander, 1976); a prospective survey in more than 23,000 women in France (Goujard, 1977); a prospective study in 19,906 pregnancies (Torfs, 1981) and a prospective cohort study in 13,643 pregnancies (Michaelis, 1983), a historic prospective cohort study in 35,114 women (Katz, 1985), a case control study in just under 3,000 women (Resseguie, 1985), a case-control study of almost 40,000 births in Spain (Martinez-Frias, 1998).

Published reviews
A number of reviews of the data have been conducted. On balance the majority of authors concluded that the weight of evidence does not support a causal association between exposure to exogenous sex hormones during early pregnancy and developmental malformations but considered the evidence to be insufficient to definitively refute such an association. Many commented on the poor quality of the epidemiological data, the paucity of data from robust prospective studies and the importance of adjusting for the effects of susceptibility bias and confounding factors (WHO 1981; Wilson 1981; Horowitz 1985; Martinez-Frias, 1998).

Despite the limitations of the majority of the individual studies some authors concluded that there was some evidence in support of a connection between exogenous sex hormones in early pregnancy and a small increase in cardiac defects, although firm conclusions on causation were not possible (Shapiro 1979; Polednak 1985). Some argued that if a causal association existed the level of risk would be small and there would be no way to state with certainty that a particular non-genital organ malformation was due to exposure to sex hormones in an individual pregnancy (Wilson, 1981).

Characteristics of teratogens
The available evidence for a teratogenic effect of HPTs has been discussed in the context of the characteristic features of known teratogens. These features include:

1. having a discernible effect in animal models;
2. demonstrating a dose relationship;
3. causing a unique group of malformations; and
4. being biologically plausible.

With the exception of virilisation of female fetuses, we are not aware of any animal model that has identified a teratogenic effect of HPTs, even at doses up to 1000 times the human dose equivalent of the hormones used in Primodos (Hendrickx, 1987). Furthermore, there is no apparent rational scientific explanation for the effects that have been observed in some of the observational studies and no clear evidence that exogenous female sex hormones can induce indirect responses to any other than their target tissue. Similarly there is no evidence that sex hormone receptors exist anywhere within embryos of ages which would be teratogenically susceptible to defects of the brain, heart, limbs etc. It would seem implausible that a teratogen would produce in isolation one type of malformation in one observational study and different types in others.

The London Programme
The DVD of a 1978 version of the London Programme, that was ultimately never televised, was provided by Yasmin Quereshi MP. This was a balanced programme that showcased the difficulties experienced by a few families following use of the

mother in pregnancy to HPTs. It set the scene with respect to the availability of alternative non-hormonal pregnancy tests and discussed some of the key early epidemiological data - primarily the research of Gal in 1967. It also described action taken by the Government and the Marketing Authorisation Holder, Schering, in response to these data and the changing environment.

No new data was presented and no information that would alter the overall conclusions of this review.

Conclusion
Having carefully considered the available published evidence, our position remains that the data are not sufficient to conclusively prove the existence of a causal association between the use of Primodos (or any HPT) and congenital abnormalities. The evidence for congenital cardiac defects is perhaps the most persuasive but even here, the data are conflicting, relate to a number of different defects and the majority of the studies have limitations that would affect the reliability of the findings.

Given the multi-factorial reasons for prescribing and using HPTs, it is not difficult to envisage that women who used them could differ quite substantially from those who did not and that incomplete adjustment for these differences alone could give rise to the observed associations. Some of the better-designed studies provide more robust evidence but by themselves do not allow firm conclusions to be drawn.

While it is entirely understandable to suspect that there may be an association between a medicine and a condition that develops after taking it, this may not necessarily be the case. The time between the medicine being administered and an adverse outcome is only one factor that needs to be considered. There may be other factors, possibly not even known at the time of study (such as the importance of folate intake and NTDs) which mean an adverse outcome would have been observed regardless of whether the medication had been administered.

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Appendix 1 – Summary of historical evidence

Author (date)	Study design	Subjects/ participants (n)	Product	Objective	Primary outcome measure	N (events per exposed cases)	Results RR/OR	Authors' conclusions	Assessor comments
Higgins; 1960	Primodos provided to all women presenting with short duration amenorrhoea between August 1959 and March 1960	12 women – 4 tablet test 47 women – 2 tablet test Exclusion of women who were obviously pregnant	Primodos [2 tablet test; NETA 5mg/EE 0.01mg 4 tablet test; NETA 10mg/EE 0.05mg]	To determine the long-term accuracy of Primodos in diagnosing pregnancy	Pregnancy/non pregnancy Abortion Rate of abortion	4 abortions in 43 pregnancies (authors calculate expected rate of 8-9 in 43 pregnancies)	NA	Abortions could not be definitively attributed to the drug. Primodos is a simple safe accurate test for pregnancy	Limited methodological details; no comparator; relatively small number of exposures. Strength – all women exposed irrespective of previous experience Desirable to have control group which is as comparable as possible and studies in a comparable way. Other risk factors not mentioned
Dubowitz, 1962	Case report	1 woman	Amenorone HPT (ETA 10mg/EE 0.01mg (1 tablet x 3 days)	NA	Virilisation of female infant		NA	It is only possible to speculate whether there is any correlation between ETA/EE and the abnormalities. The use of progestogens during pregnancy do not invariably result in virilisation – it may be that factors other than dose, stage of pregnancy, and possible variations in the placental permeability to steroids and the maternal metabolism of steroids are of major importance in determining the response to a drug.	Single case report of virilisation – ETA/EE not NETA/EE and different dosing schedule. Single case reports are of little value: 2-3% of all infants have deformities recognizable at birth
Jacobson; 1962	Case reports from single practitioner	385 consecutive private obstetric patients	Norethindrone (norethisterone) Oral doses of 10-40mg for 4-35 weeks of pregnancy	Efficacy in management of threatened abortion	Maintenance of pregnancy Virilisation of female fetus	15 of 82 female infants (18.3%) born with affected external genitals vs 1% in untreated women. 24% when treated 1st trimester; 4% 2nd-3rd trimester; 15% at doses of 10-20mg; 29% at doses of 25-40mg; 50 abortions	NA	NETA useful in treating threatened abortion but is not a preferable agent to use because of issue of long-term administration and virilisation.	Non-randomised, non-comparator (non-treated group but not matched) ; progestogen only; far higher dosing regimen; product given for up to 35 weeks; No apparent causal relation between past obstetric history or presenting complaint however no other factors looked at. No reports of congenital abnormalities.

Author (date)	Study design	Subjects/ participants (n)	Product	Objective	Primary outcome measure	N (events per exposed cases)	Results RR/OR	Authors' conclusions	Assessor comments
Smithells 1964	Inquiry based on prescriptions		Amenorone forte (ETA 50mg/EE 0.05mg); Primodos (NETA 5mg/EE0.01mg)	To investigate teratogenicity of HPTs	Virilisation	189 prescriptions were given in weeks 1-12 of pregnancy. 186 births were normal, twins were born with patent ductus arteriosus (Amenerone Forte on d55) and one had systolic murmur (Amenerone Forte d40, rubella 8th week)	NA	Provides no evidence to support HPTs as teratogens. A teratogenic agent is likely to produce a limited number of different malformations rather than a whole range of deformities.	Small sample size; lack of information
Gal, 1967*	Retrospective case control study	Mothers of 100 babies born with meningomyelocele or hydrocephalus and 100 healthy babies	Amenorone forte (ETA 50mg/EE 0.05mg); Primodos (NETA 10mg/EE0.02mg)	Survey to investigate factors during pregnancy contributing to fetal abnormality	Meningo-myelocele, hydro-cephalus	19 cases and 4 controls used H PTs	NA	The observations indicate the need for a more detailed scrutiny of the role of hormonal preparations in the causation of congenital malformations, particularly when taken in the organogenic stages of pregnancy.	Retrospective survey with healthy babies as control therefore possibility of recall bias (but medicines checked with physicians); effect of HPT not primary objective of study; other questions asked not specified; pregnancy diagnosed quicker in cases (5.6 vs 6.2 weeks) suggestive of urgency/difference in obstetric history in cases? How cases and controls were 'matched' is not specified. Finding could be due to chance as a number of epidemiologic factors were studied. Method of determining time between conception and HPT not clear. Biological plausibility questionable. Folate intake not considered.
Robinson 1970	Retrospective matched cohort	1,250 cases (COCs use); 1,250 controls (never-COC user) matched by age 458 pairs matched for age and parity	COCs			85 abnormal case pairs vs 61 abnormal control pairs (p>0.05) No effect of duration of COC use 46 women used COC during pregnancy (up to 5 months)		No statistically significant difference in frequency of abnormalities between cases and controls. No suggestion of significant degree of risk in terms of life-threatening or serious disorder of structure or function in subsequent progeny	Matched by age and parity only Controls had never used COCs – these women are likely to be very different in some important way to women who did use COCs, particularly at this time – reason for COC use not known. Other confounding factors not considered, including previous obstet/medical history (other than parity). Composition of COC unknown. No information given about why final 458 pairs were chosen.

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Laurence 1971*	Retrospective case control - 1968-1970	271 cases (spina bifida and anencephaly); 323 controls (no neural tube defect, NDT) from 3 centres: In one area controls were next baby born in the same hospital; in another mothers were matched for area of birth, parity and month of conception; in the other mothers had one baby with NTD and a normal birth during the study period.	HPTs (O+P)		Neural tube defects	8.1% of cases had HPT vs 6.8% of controls	NA	No sig association between HPTs and neural tube defects.	Relatively large numbers; more matching than previous studies (parity, age and location in some cases) although other risk factors such as maternal age not matched for – also for London series there's no matching.; meningomycele and anencephaly evaluated separately and no suggestion of association for either. Other possible confounding factors, including previous medical history and reason for HPT not taken into account. Broad definition of HPT – no specific product.
Gal 1972*	Retrospective case control 1965-6	100 cases with spina bifida, admitted consecutively to two hospitals for surgical treatment; 100 healthy controls (same number as cases collected each week to account for seasonal differences in spina bifida). Matched by mothers' age (5 yrs), reproductive history (no pregnancies, abortions, history of infertility), course of pregnancy (bleeding, hormone treatment, duration and type of delivery) sex of baby. General health, drug intake, family and medical history taken and validated with GP.	Primodos [10mg NETA/0.02mg EE] and Amenorone forte [50mg ETA/0.05mg EE]	Possible cause of central nervous system malformations	Spina bifida	19 HPT cases; 4 controls	P<0.001	HPTs might have caused or acted as the trigger for spina bifida in 1 in 8 cases.	Relatively careful matching (not all risk factors accounted for e.g. folic acid status, alcohol, maternal nutritional status, genetic factors, socioeconomic factors, comorbidities); attention paid to effect of reproductive history; high level of significance when all predisposing factors excluded – but many other factors not considered and unclear how many women left (ie sample size)
Spira 1972	Prospective cohort study	20,000 French women followed from 3rd month of pregnancy to 1 month post pregnancy.	9,566 used sex hormones during first 3 months as HPT or supportive therapy		Serious mal-formations	171 (1.8%) children with serious malformations in exposed women - did not exceed the 2% observed in 8,387 unexposed pregnancies.		No association between sex hormones and serious malformations	Study described in Wilson 1981
Laurence 1972*	Critique of Gal 1972	See above	See above	See above	See above	See above	See above	Cases drawn from wide area of Southern England; matched controls from one hospital – differences could be accounted for by prescribing practices.	Sever suggests possible prescribing bias in Gal 1972 study.

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Sever 1973*	Re-examination of Gal 1972 data	See above	See above	See above	See above	See above	See above	Since cases were meningomycele, exposure to a teratogenic agent needed to have taken place before closure of the neural tube at day28 (week 4) of gestation. Gal states that the average time from conception to HPT was 5.6 weeks (39d), which implies that a large proportion of cases must have been exposed after the critical period of organogenesis.	Questions biological plausibility of Gal's findings; however accuracy of conception date?
Nora 1973	Retrospective case control	224 women with congenital heart disease (CHD) 262 controls	Any O+P as oral contraception or HPT			20/224 vs 4/262 exposed during vulnerable period	P<0.001	Of 12 patients with VACTERL 8 had exposure to O+P or P at a vulnerable time during organogenesis. Accept deficiencies of retrospective studies and recommend a prospective study.	Retrospective therefore recall bias?; no info on matching of cases and controls; no info on type of hormonal exposure (dose, product, indication, duration, time of gestation etc) although the title of the article would suggest these were oral contraceptives; no info on possible confounders
Levy 1973	Retrospective case control	76 cases with TGV; 76controls with mendelian disorders Matched by birth date	Any hormone	Hormone treatment during pregnancy and TGV	TGV	7 to any hormone during 1st trimester (6 within first 6 weeks for threatened abortion and 1 P for HPT) 0 controls	P=0.007 Fischer's exact	CHD thought to be multifactorial but hormonal treatment during pregnancy may be a predisposing factor.	Recall bias limited due to controls having defect; in addition to hormones cases also had other risk factors (2 diabetic, 1 oophorectomy in 3rd month due to ovarian cyst). 9 controls had vaginal spotting in first trimester but none treated. Not specific for HPTs but result for HPT (1 vs 0) not significant; no mention of other risk factors and no information on similarities or differences between other risk factors Stimulated by Nora & Nora letter
Oakley 1973*	Retrospective survey of cases 1970	433 mothers of infants with a range of congenital malformations	Any HPT		NTDs, Cleft lip +/- cleft palate, cleft palate, Down's syndrome, oesophageal/ intestinal atresia, omphalocele, diaphragmati c hernia, limb reduction deformities, multiple mal-formations, other syndromes	46 (10.6%) received HPT in first trimester Proportion of women receiving HPT in each malformation group did not differ from the proportion as a whole.		Similar proportions of HPTs in all defect groups may mean that they are not associated with malformations. Alternatively they cause an increase in all defects, which is unlikely on biological grounds. The number of NTD cases was sufficiently large to make the negative findings reliable. For other defects the numbers were too small to be robust. High frequency of HPT use in cases of oesophageal atresia-warrants further study	Retrospective survey 3 months post-partum hence recall issues; use of hormones to confirm pregnancy not validated through medical records; no controls or background rates; large numbers of NTD cases; many risk factors not accounted for; Down's syndrome, a chromosomal disorder determined prior to hormonal exposure, occurred in a similar % (9.7%) as did other malformations – suggests that pregnancy tests not causally related to malformations (Wilson et al, 1981)

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Nora and Nora 1974	Prospective cohort study and commentary	See Nora and Nora 1975	See Nora and Nora 1975	See Nora and Nora 1975	See Nora and Nora 1975	See Nora and Nora 1975	See Nora and Nora 1975	If hormones produce deformities it is at a low rate, probably acting on pre-disposed women. Prospective studies must contain large numbers of patients and will take up to 3 years to do. Retrospective studies are limited because they are reliant on the accuracy of the primary input of data. Adequate teratogenic histories do not appear in medical records – one third of patients who stated using hormones did not have this recorded in medical charts. Hormone use is understood/ remembered/reported poorly by women. Quick and dirty retrospective studies are likely to be uninformative or erroneous.	
Janerich* 1974	Retrospective case control study starting 1968	108 cases; 108 controls matched according to race and age (2 yrs) of mother; selecting adjacent birth records for controls meant that case and control groups same in mother's county of residence and baby's dob Single interviewer	Any exogenous hormone	Exogenous hormone exposure during pregnancy in relation to congenital limb-reduction defects	Congenital limb reduction defects (LRD)	Combining any use of hormones during pregnancy: 15/108 exposed cases vs 4/108 exposed controls. 3 HPT exposed cases vs 1 exposed control Possible association with twinning and defects and socioeconomic class and defects also identified.	Use of any hormone P<0.02	Data confirm association between exogenous hormones and limb deficiencies but not clear whether it is causal or secondary. No specific hormone or product specifically associated and unaware of definitive evidence. Some sort of maternal predisposition (eg hyperactive reproductive system) is probably necessary before exposure can lead to a malformation.	Identified recall bias when recalling use of OC – arguably applies to HPT use. This is potentially increased by use of controls that are normal children and long delay from birth to interview in many cases. Difference in use of HPTs between cases and controls not specified but unlikely to be significant – very small numbers; identified other possible risk factors i.e. twins, parity, socioeconomic class Two children exposed in first month of gestation when risk of LRDs low; 5 sets of twins in malformed group – a known risk factor; both unilateral and bilateral cases included – unilateral defects more likely caused by vascular disruption or genetic anomalies. Under-ascertainment of sex steroid exposure in control group. No recognisable pattern of events or syndrome (LRDs involving multiple mechanisms and etiologies included).

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David 1974*	Retrospective ecological case study South West England 1942-1973	345 cases of atresia. Looked at trends over time and against sales of OCs and HPTs	Primodos, Amenerone, Orasecron OCs		Oral hormones in early pregnancy cause oesophageal atresia – alone or as part of VACTERL	No cases of VACTERL identified out of 345 atresia cases. No linear trend over time for cases.		Do not support the suggestion that oral contraceptives or oral HPTs cause oesophageal atresia alone or as part of VACTERL	Very sparse methodology; ecological study with all its limitations.
Haller 1974 (In German)	Prospective cohort study	3,588 women: 617 HPT 377 threatened abortion	COC, HPTs	To investigate possible correlation between a number of hormonal treatments (for different reasons) and abnormalities in their offspring		Abnormalities in HPT users vs non-users: 2.6% vs 2.1%, ns

In threatened abortion users vs non-users: 1.9% vs 2.2%, ns | Not significant

Not significant | No association between HPT or hormones for abortion and abnormalities | Full details not available in English |
| Nishimura 1974 | Examination of live induced abortuses of mothers exposed to sex hormones | 397 exposed - 4-8 week embryos and 69 8-20 week embryos – exposed to hormones Controls 5,261 embryos and 526 early foetuses with no exposure | P+/-O | | General mal-formations in all and CHD in 6-7.5 wk. embryos | 2% malformation in exposed 4-8 week embryos and 4.3% in 8-20 week ones

2.1% in control embryos and 3.2% in early foetuses

TGV 0 in exposed vs 4 in controls | No difference

No difference

Could not exclude RR<13 due to small numbers | No increased occurrence of external malformations. | Abstract only so sparse details. Some evidence for lack of major generalised effect |
| Mulvihill 1974 | Retrospective case control 1968-73.

Identified all children with TGV or single ventricle at <5 years old in the John Hopkins Children's Cardiac Centre. | 88 cases with TGV or single ventricle; controls patients with ventricular septal defects (VSD) alone and with normal hearts, matched by sex, race, age and year of first visit.

Information on sex, race, birth date, age when first seen, all birth defects and pregnancy history obtained from medical charts. | Progestational agents | To investigate whether progestogens are causally related to TGV | TGV or single ventricle | 4/88 cases exposed (2 threatened abortion, 1 birth control, 1 fertility) vs 5 VSD and 4 normal hearts (mostly threatened abortion). | | Do not support a causal relationship with cardiac defects. | Info extracted on sex, race, birth date, age when first seen. All birth defects and pregnancy history. – however no info on these factors. Methodological details too sparse to draw conclusions about validity of results. Results could be due to chance – however investigators included 19 children who had diagnosis of single ventricle as cases of conotruncal malformation– had these been excluded the data would have been consistent with a teratogenic effect (from Shapiro 1979) |

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Brogan 1975*	Retrospective cases study in Australia 1963-1974	222 cases with cleft lip and palate	HPTs	To investigate maternal histories during first trimester and parental histories prior to conception.	Cleft lip and palate	22 (10%) received oral or parenteral HPTs between 5-8th week of gestation.			No control group therefore no conclusion can be drawn. In HPT user group 18% had planned their pregnancy; in total group 54% of pregnancies were planned; This could suggest that HPTs are used more frequently to diagnose pregnancy that is not desired – possibly for inducing a miscarriage.; other risk factors not included
Harlap 1975*	Prospective record-linkage cohort study Jerusalem 1966-68	11,468 babies in total (64% of total number born in that period); 432 (3.8%) born after definite **or probable** administration of oestrogens or progesterones.	COC, HPT	To re-evaluate the safety of O + P in early pregnancy	Minor or major congenital mal-formations.	47 had one or more major or minor malformation, (109/1000 exposed vs 78/1000 with no history of exposure 9 women had taken the pill or HPTs and produced no mal-formations. 29 women had used hormones as abortifacients and in 3 there were minor mal-formations. 100 born after exposure to unspecified drugs (could be hormonal) to guard against miscarriage – 8 mal-formations.	P<0.02	Risk of major malformations is about 26% higher in group exposed/probably exposed to hormone; for minor malformations the increase is 33%. Part of the increase in risk may be due to teratogenic effects of these hormones.; need to re-evaluate safety of therapeutic hormones- particular important since women with abnormal sex-hormone metabolism may be more susceptible to the teratogenicity of exogenous hormones.	?accuracy of exposure history- 100 women were given drugs to protect against miscarriage which were assumed to be mostly hormonal though this was not stated. Confirmation of exposure could therefore completely alter the findings. Since it is a prospective study usual biases of retrospective studies of malformations are avoided; specific drugs not looked at; Even if only 1.5% inaccuracy ie an additional 170 of the 11,032 women took hormones the incidence of malformations in both groups would be the same; data do not take into account conditions for which a mother would be given exogenous hormones; important risks factors not looked at. Findings may be confounded as the drug was sometimes given for threatened abortion which itself maybe have been a risk factor for cardiac malformations (from Shapiro 1979)
Greenberg 1975	Interim analysis retrospective case control in England and Wales 1971-2	Controls (no congenital malformations, born in same GP practice within 3 months) 836 pairs of cases and controls.	HPT		Variety of deformities	23 of 149 cases (15%) vs 8 of 149 controls (5%)	Ratio of case to control exposure 2.09, P<0.01	Supports the recommendation that there is little justification for continued use of HPTs	See Greenberg 1977

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Jaffe 1975	Retrospective review of all limb-reduction abnormalities born at Northwick Park hospital between 1972-1975	7 cases Information on cases from parents, GP and hospital records. No history of congenital deformity, all Caucasian	Sex hormones		Limb reduction defects	I case exposed to NETA 1mg/EE 0.05mg OC still 2 months before conception 1 case exposed to oral NETA for 1 week at 3 months for threatened abortion No other cases exposed Neither of exposed cases were male (in contrast to Janerich) Clustering in Jan/Feb and July/Aug	Incidence 1/1000 compared with 0.2/1000 from a NY study	No common predisposing factor has emerged from review of the cases.	Large sample size of births; unfair comparison to NY study as that included the whole of NY surveillance program compared to only one hospital in this study. 2 cases exposed to HPT – 1 at 2 months before conception and 1 at 3 months – so not during critical periods. Also 2nd case had urinary infection at 4 weeks and was given co-trimoxazole – possible risk factor? When 11 cases of Down's syndrome were deducted from malformed group no meaningful difference (Wilson et al, 1981)
Nora 1975*	Retrospective case control	15 cases with at least 3 major anomalies of VACTERL group vs 15 controls with chromosomal abnormalities matched on age, race, socioeconomic level, area of residence and 30 controls with murmurs clicks or benign cardiac findings.	EE or EE+P mainly for HPT, OC or threatened abortion		At least 3 major anomalies of VACTERL group	13 of 19 VACTERYL cases exposed to hormones of which 6 to HPTS, 5 NETA/EE or mesantrol and 4 MPA 9 of 15 cases exposed to EE+P vs 2 of 15 chromosomal controls and 3 of 30 murmur controls	P<0.025 P<0.005	This cluster of patients suggests the possibility that EE+P is teratogenic and associated with the production of anomalies involving many systems. Subtle and unrecognized biases could easily have distorted the findings. Prospective study using the National Institute of Child Health and Development will provide substantive base for reliable conclusions.	Update to the 1973 report in 12 patients. HPTs were taken to diagnose pregnancy and 'for a variety of other reasons'. Doses, timing and frequencies of exposure all different. Drug history taken as long as 6 years post birth in cases and controls therefore recall bias. Accuracy of exposure also questionable as women were subject to "considerable probing" if the initial answers were negative regarding hormone intake and confirmatory data on exposure not found in more than half of charts. Furthermore questionnaires failed to disclose positive histories. All patients were from one area thereby reducing prescribing bias. Authors mention that they have collected data on exposure to O+P at the vulnerable stage of organogenesis in women who have delivered normal infants. Sample comprises 317 women, 24 (7.6%) who had O/P at some time during pregnancy and 10 of whom were exposed during organogenesis (3.1%).
RCGP 1975	Prospective cohort study of pregnancy	9,474 women studied 8,255 pregnancies >28 weeks		Possible role of maternal morbidity and its therapy in aetiology of congenital malformations	Normal outcome, lethal mal-formation, doubtful mal-formation, rhesus in-compatibility, other stillbirth	3% of all births were lethal or had unequivocal malformations. Of these 48 (20%) had no drugs and 80% either had drugs alone (48; 20%) or in combination with morbidity (149; 60%)	No cause and effect relationships were identified for individual drugs using source records (hormones not specifically investigated).	There is no evidence that drugs in common use with early pregnancy as a whole have any correlation with subsequent malformations in the child, however, adverse effects from rarely prescribed drugs cannot be ruled out.	Other factors looked at: previous abnormal pregnancy outcome only

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Dillon 1976	Case series 1964-76	13 abnormalities	O+P in 5 cases – 2 EE/NETA HPT P in 9 cases		Congenital abnormality - any	1 use as COC; 8 previous abortion; 2 HPT (4th and 6th week); 1 polymenorrhoea	Case 1: Spina bifida/hydrocephalus – HPT 6th week Case 2: TGV – HPT 4th week	In the case of HPTs and P used for threatened abortion the critical period could well be past when the woman is exposed. In the gp exposed to P, it could be that fetus who would otherwise have been aborted were salvaged.	Small number of case reports; re the first statement – depends what congenital malformation is being looked at.
Hellestrom 1976*	Retrospective review of 32 cases of limb reduction abnormality 1965-74	Cases asked about exposure to HPT, OC failure, threatened abortion in first 3 months; 30 controls with spina bifida born during same period	HPT, OC, threatened abortion		Limb reduction deficits	3 cases exposed to HPT and 4 treated with hormone vs 1 control HPT plus threatened abortion		Study too small to be conclusive but results point towards an association	Cases and controls same with regards to parity and exposure ; Parental recall of drug exposure; sample size too small; only descriptive analyses; other risk factors not taken into account;
Kullander 1976*	Prospective study of 6,376 pregnancies 1963-5, Sweden	5002 normal pregnancies 551 minor malformations 194 major malformations	Gestogens Primodos	Possible role of hormones in human fetal mal-development	Any outcome	156 women received Primodos during weeks 4-8 of amenorrhoea. Miscarriage 3.3%; Induced abortion 8.4%; Birth 2.2%; Normal 2.2%; Dead 0%; Minor defect 2.9%; Major defect 2.1%	Of 5002 normal babies 98 (2%) had received gestogens during the first trimester Among 551 minor malformations 9 (1.6%) had received gestogens. Of 194 major malformations 5 (2.61%) received gestogens. Of the 15 hypospadias and 11 CNS none received gestogens	No teratogenic effect could be observed with gestogens. For Primodos, the figures do not exclude a teratogenic effect but they give no support for it. A weak correlation can be found between the use of sex steroids and congenital anomalies. In this study gestogens were more often prescribed if bleeding had occurred early during the pregnancy or if previous reproductive failure had occurred. Both are associated with the birth of more malformed infants than normal.	Large sample size; no comparator other risk factors not mentioned; authors suggest indication bias due to prescribing of gestogens in women with bleeding during early pregnancy.
Gal 1977	letter							Suggests that the range of abnormalities seen reflects differing stages of gestation when exposed to hormones - similar to that of other powerful teratogens.	In observational studies where hormones are not given at any fixed time during gestation such an effect wouldn't be seen. By contrast observing a single type of malformation in women taking sex hormones at different times throughout pregnancy seems implausible.

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Goujard 1977*	Prospective survey, 12 hospitals in Paris, 1963-1969	12,764 women in cohort 216 cases - unequivocal malformations 11,225 controls – normal live born infants	P/O in first trimester – mainly used as HPT		Major anomalies (CHD, skeletal anomalies, (VACTERL not encountered)Microcephaly	1.6% (160) – no hormone 1.5% (5) – testosterone deriv. 1.8% (15) – progesterone deriv.	Rate of malformations no different between exposed (either progestogen derived or testosterone derived) and unexposed mothers. For individual outcomes microcephaly was high in cases (3.4/1000) vs controls (0.6/1000); p sig at 1% CHD: 4.29/1000 vs. 4.07/1000 Skeletal anomalies: 4.29/1000 vs 5.29/1000	No definitive evidence for the teratogenicity of HPTs – any risk is small.	Prospective study – so recall bias avoided; standardised questionnaire used and Px and self-medication were carefully recorded by a detailed interview; Controls assumed to be from same hospitals as controls?; Risk factors at baseline not taken into account?
Greenberg 1977	Retrospective case control England and Wales, 1972-1977	2,867 cases initially of which only 836 (29%) were followed up– voluntary reporting of visible and severe malformations Controls - normal baby born in same practice within 3 months	HPTs not specified	Identification of possible teratogens	NTD, oral clefts, limb mal-formations, other	Number of prescriptions for any drugs was equal between cohorts. Between cases and controls: mean age, history of miscarriage, average number of births, average number of previous pregnancies was similar. History of congenital malformation in family of cases was much higher than in controls (14% vs. 3%) 73 case vs 35 control If exclude women with history of malformations (67 vs 35)	Ratio cases: controls 2.1; p<0.01 Ratio cases: controls 1.9; p<0.01	Abnormality in the study families was much higher in cases but excluding these mothers shows that this cannot account for the effect associated with HPT. Results consistent with general teratogenic effect of HPTs but do not suggest a specific effect on the neural tubes. The excess risk was not great and association with malformations was nonspecific.	Well designed, matched study, careful attention to possible bias and past obstetric history. GPs asked to provide morbidity and exposure history from written notes; abnormality reporting voluntary therefore incomplete?; selection of controls eliminates prescribing bias but controls were normal therefore recall bias?; cases and controls not matched other than birth date, location and GP; un-blinded questioners and respondees; although only 29% of cases were included the reasons for exclusion should not introduce bias; cases 23% folic acid supplements vs controls 29% Not designed to test the hypothesis that HPTs were teratogenic

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Heinonen 1977*	Prospective cohort study	50,282 mother-child pairs in 12 US hospitals, 1958-65. Extensive information on drug exposure during first 4 months of pregnancy, maternal illnesses, complications of pregnancy collected – drug use confirmed by physician or records. Examination by cardiologist – blinded to exposure		Association between antenatal exposure to female sex hormones and cv birth defects further evaluated.	Cardio-vascular defects	Sex hormones used by 1042 women; 438 used E+P, 176 used E and 428 used P. Of these 19 had cv defects (18.2 per 1000) vs 7.8 per 1000 in controls, crude RR 2.3.\n\nAdjusted RR of 2.1 for O+P; p<0.05\n\nRR 1.4 E only; RR 1.5 P only NS\n\nRR OCs RR 2.4 (subgroup of E+P) NS	Characteristics of exposed women different to unexposed therefore multivariate analysis used.\nVaginal bleeding, history of abortion, stillbirth, death not associated with cv outcome. The ratio of observed children affected vs expected gave relative risk estimate, adjusted for confounding (including effect of other drugs).	Results provide further evidence that female hormones taken in the early stages of pregnancy may disturb the normal cv development of the fetus.\nAdjustment for confounding tended to reduce the strength of the association and there may have been further factors of relevance that were not taken into account.\nSuspicion that association is causal strengthened – exposure after 4th month gave no evidence of association.\nObservation required confirmation.\nSeparate and combined role of hormones needs to be clarified.	Well-designed, prospective, blinded, confounding factors considered. Looked at duration of exposure –only increase in risk for exposure up to 4 months. No information on indication provided,; 5 cases exposed during weeks 1-2 when no risk to fetus. . 2 Down syndrome, 3 where exposure in 4th lunar month. 4 exposures in 1st lunar month – exposure occurred before conception (Wilson 1981). Only 4 cases possibly HPT? Only 1 EE+NETA (norethindrone)\nNot clear whether women in control group were similar to those treated in terms of factors taken as indications for hormonal treatment, such as presence/absence of history of recurrent abortion or threatened abortion in present study as these may be important risk factors for abnormal pregnancy outcome.\nIn subsequent publication in "Birth defects and drugs in pregnancy" 1977, authors state no significant association observed for congenital limb reduction defects or VACTERL. Association with cv malformations highest but not sig with OCs. MPA was only specific hormone with a stat sig association. Exposures most likely to be for threatened abortion.\nNo individual drug carried increased risk but numbers small.
Janerich 1977	Retrospective case control 1971-4	104 infants with a birth certificate mentioning CHD. Interview procedure as previously described with GP blinded to exposure status. 104 controls - next birth certificate chronologically in that county, matched to case on mother's age (within 2yrs) and race, dob and county of residence Classification of malformation by doctor blinded to exposure.		To determine whether exogenous sex hormones during pregnancy are associated with CHD, by itself or in combination with other malformations.	CHD and other mal-formations	Of 18 exposures in cases 10 had HPTs. In controls there were 3 exposures in total of which 2 were HPTs.\nNo effect of concomitant prescribed drugs or infectious agents. HPT most strongly associated with most severe forms of CHD which tend to cause early death.	RR 8.5 p<0.001\n\nRR 7.5 p<0.001 when family history controlled for.\n\nNo noteworthy differences in baseline characteristics between cases and controls except previous live births (unexpectedly higher in case mothers).	Results support the hypothesis that sex hormone exposure during pregnancy may cause CHD – more strongly associated with multiple malformations than single heart lesions.\nRisk small - estimate that no more than 19 additional cases of CHD would be produced by a similar level of hormone use during pregnancy among a population of 100,000 births.\n\nUsing the same study procedures for matched case-control studies of other birth defects including anencephaly (66 pairs), spina bifida (135), Down's syndrome (103), hypospadias (99) no increase in the number of patients exposed to hormones was identified.	HPT, COC, supportive therapy grouped together. Relatively small number of cases. 95% CI said to be wide but not provided. Controls normal babies therefore possible recall bias.\n\nResults in other malformations suggests negative findings for non CHD defects – but it would appear these were not published ?E.g. for spina bifida – Gal et al had shown association between HPT and spina bifida and this study has not.\nMcNemar's test used – this is for paired observations – although only matched for mother's age, dob, country and race – since 98% were White matching by race does not make a difference?

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Smith 1977	Retrospective case control based on Congenital Anomaly Surveillance System in Canada 1969-1971.	93 cases from Alberta (54 of 64 reported cases 84%) and British Columbia (39 of 51 reported 76%). 2 controls per index case – 1 normal and 1 with congenital anomaly other than-limb congenital abnormality. Matched for dob (within 2 weeks), district of residence, period of gestation (within 2 weeks), mother age (within 3 yrs), parity of mother and sex of child. Parents provided info on child's deformities, family history of congenital abnormalities, record of consanguineous marriage, environmental influences, previous pregnancies and complications thereof, method of contraception.	OCs only	To determine why more infants had been born with congenital reduction deformities of the limbs in 1969	Limb reduction deficit	35 cases vs 50 normal controls and 41 abnormal controls	Peak in abnormality reports in 1969-70 and 1973-4.	Of the 136 pieces of information provided number of significant responses no greater than chance. No association with OC use. Results are reassuring and show feasibility of conducting retrospective study soon after observation of change in abnormality rate through surveillance system.	Relatively extensive information collected from parents including complications of pregnancy but validation by GP of details. Relatively careful matching. Interviews and review of data – not stated whether these were blinded to exposure status or purpose of study.
Nora 1978	Describes 4 studies – 3 case controls and one cohort. In the cohort expectant mothers were interviewed by trained interviewers as early as possible and later in pregnancy.	Cases and controls matched as closely as possible for at least sex, race and gestational age, and if possible also on socioeconomic level and area of residence. Babies from both groups were examined by HCPs blinded to exposure. Case-control study 1 – 32 cases, for 16 patients 2 patients to serve as controls who were referred for evaluation of heart murmurs. For the remaining 16 cases – children with functional murmurs but also normal births Case-control studies 2 and 3 – 236 cases with congenital heart lesions 60 matched with patients with known single mutant gene and chromosomal disorders. For 176 cases 2 control matched with each congenital heart patient. Cohort study - 118 first trimester exposed cases and 118 controls	In cohort study: HPT (15) OC (15) Threatened abortion (13)	Does maternal exposure to exogenous P and E during the first trimester of pregnancy represent a risk to the fetus? If so, how great is the risk?	VACTERL, congenital heart lesions	C-C study 1 (VACTERL) – exposed 13/30 (43%), controls 5/60 (8%), p<0.001 C-C study 2 (congenital heart disease) – 14/60 (23%) vs. 3/60 (5%) controls with genetic disease, p<0.005. C-C study 3 - 31/176 (17.6%) vs. 21/352 (6%) Cohort study – 11/118 (9.3%) exposed cases had major malformations vs 4/118 (3.4%) controls,	C-C study 1 – RR 8.41 for VACTERL C-C study 2 – RR 5.58 for CHD CC study 3 - RR 3.55 for CHD Cohort study - RR 6 for CHD and 2.75 for occurrence of major malformation Chi squared values of 3.7 (p 0.055) for CV anomalies and 3.5 (p 0.062) for major anomalies.	Because of the fall in HPT use, there were insufficient cases to address the question. But recognise the biological significance of the data. Nevertheless, the association of hormonal exposure with VACTERL provides the strongest evidence likely to become available from retrospective studies. The statistical differences are highly significant. By contrast a search for rare single anomalies has proved equivocal. Two of three prospective studies provide evidence consistent with an association between exogenous hormones and congenital heart disease; one does not. A 2-4 fold range of increase may be projected by combining the two positive studies. Furthermore, the weight of evidence from studies conducted by several groups supports an association.	Number of cases too small for statistical significance. Two of the 6 cases of cv defect involved only patent ductus arteriosus – this is not a malformation but a postnatal functional persistence. No evidence that it relates to any structural or functional defect induced in first trimester. The reason for hormone administration stated in only 45 cases, no adjusting for confounding factors. Little information on the timing of exposure

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Rothman 1979	Retrospective case control study.	Cases infants with CHD born in Massachusetts 1973-5. Controls 1500 births selected randomly from all births in the same county during the same time. 460 cases (402 live and 58 dead). Questionnaires mailed to all cases and controls except the mothers of dead babies who were telephone interviewed. No confounding according to parity, maternal age, education and insulin use.	HPT, OC	To evaluate the effect of hormonal exposure before or during pregnancy on the risk of congenital heart disease.	CHD	92% of cases and 89% of controls responded. Drug use during early pregnancy – 54% cases vs 41% controls. Small positive association for each of OCs, HPTs and progestogens. Individually each was compatible with sampling variability; combined RR 1.5 (1.0-2.1).	HPTs strongly associated with total anomalous pulmonary venous return, prevalence ratio 11 (1.9-45) based on 2 cases Trunco-conal defects as a group or individually were not associated with hormone exposure.	The data suggest with 95% confidence that the association between hormones and CHD is characterised by a prevalence of <2.1, and with trunco-conal defects <2.0. Exogenous hormones, if they cause an increase in CHD, probably cause only a modest increase	Cases and controls unmatched but confounding estimated by stratification according to limited number of factors Cases and proportion of controls interviewed differently. Comparison of drug histories in all diagnostic categories of cases to overcome recall bias (using other cases). Due to recall, uncertainty in determining what gestational week the drug was taken. High and relatively even response rate for cases and controls. Relatively low exposure during study period? 90% CIs calculated. Normal control babies - possible recall bias?
Shapiro 1979	Review of published literature			Review of evidence linking use of female hormones in pregnancy to various effects in fetus, including neoplasms, malformations, spontaneous abortion, prematurity and perinatal death				CHD – the weight of the evidence points to a connection between female hormones (any) in early pregnancy and CHD. NTD – the evidence to support the hypothesis is conflicting but there are grounds for suspicion and further studies are needed. Limb reduction deficit – independent confirmation of this hypothesis is needed. VACTEL – evidence for existence of the syndrome are equivocal and if it does exist its association with hormones can be questioned on methodological grounds that include inadequate numbers and possible selection bias.	
Ferencz 1979	Retrospective case control in Maryland State Intensive Care Neonatal Program area.	110 infants with conotruncal cardiac malformation 3 controls from birth population for each case (1 matched on 8 maternal factors related to likelihood of taking hormones; 2 matched on these plus infant's sex and birth weight; 3 chosen at random).	Exogenous female sex hormones	Association between exogenous hormones and conotruncal malformations	Conotruncal cardiac mal-formations	COCs: 9.1% in cases vs 3.4% or 7.6% or 6.0% in control groups 1-3 respectively HPTs: 3.6% cases vs 5.1% or 7.6% or 3.4% in controls 1-3 resp. Progestogens: 4.5% cases vs 2.5% or 3.3% or 7.7% for controls 1-3 resp.	Complete ascertainment avoided referral bias. Recall bias validated through physician's records and regression analysis of time since birth to interview.	Multilogistic regression analysis controlling for matching variables and scores for reproductive malformation and exposure risks revealed no association of prenatal sex hormone exposure and conotruncal heart disease	No increase in risk. However, abstract provides sparse details. Timing of exposure/gestational age not presented. Identification of hormones aided by display of pills and packages. Validation by physician's records and regression analysis on time elapsed since infant's birth revealed no differences in maternal recall over time or between cases and controls – hence no recall bias.

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Schardein 1980	Review of literature							Seems little doubt that hormones have an inherent androgenic potency that can masculinise certain female tissue of which NETA is one of the more potent agents. Realising the limitations of the published studies, when all present data are considered there seems no justification for undue concern over the induction of non-genital malformations through hormone use in pregnancy.	Employee of Warner Lambert Dept of Toxicology.
Wilson 1981	Review	Four sources of data that would indicate a potential human teratogenesis: Ia – agent produces unique group of malformations. HPTs associated with array of diverse associations. Ib – associated with increase in malformations in exposed population. HPTs have not increased malformations with exposure. Marked diminution in exposure has not results in decrease in incidence. Insufficient positive epidemiological studies. 2. Bona fide animal model – no model when sex hormones administered at therapeutic level. Various observed malformations have not been observed in any animal model. 3 Dose relationship in animals – massive doses of sex hormones can be given without any demonstrable non-genital effects 4 Reasonable biological explanation – no support for this.						Conclude that use of exogenous hormones during human pregnancy has not been proved to cause developmental abnormality in non-genital organs and tissues. The quality of epidemiological data does not, at this time, permit a definitive conclusion that sex hormones under as yet undefined conditions have some adverse effect on human prenatal development. If there are risks they are very small, may not be causal and are substantially below the risk of spontaneous malformation. Even in a malformed exposed population the vast majority of malformations could not be attributed to sex hormones. Even positive associations have been of low order of magnitude. Janerich stated that "at best of 100 congenital heart patients only 1/100 might be due to sex steroid exposure". In reality there is no way anyone could state with certainty that a particular non-genital organ malformation was due to a sex steroid exposure in an individual pregnancy	Provides a good summary of the limitations of retrospective studies. Provides mechanistic argument for a lack of effect whereby a sex hormone would only be expected to affect an organ that possesses no receptors. There is no evidence that sex hormones can induce indirect responses to any other than their target tissue and no evidence that sex hormone receptors exist anywhere within embryos of ages which would be teratogenically susceptible to defects of the brain, heart, limbs etc. Although some have suggested that excessive doses of sex hormones can result in an abnormal endometrium the pre-implanted and early implanted embryo is subject to an 'all or none' phenomenon as regards outside influences and while susceptible to death during the first 2 weeks of pregnancy is resistant to being malformed..

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Torfs 1981	Prospective using Child Health and Development Studies population who were members of Kaiser Foundation Health Plan	All women reporting for prenatal visit in the area between 1959 and 1966 who expected to deliver at the Kaiser hospital were asked to participate. Acceptance rate close to 100%. Pregnancies observed over time. Records for diseases and diagnoses and medicines abstracted beginning at 6 months before their LMP.

19,906 pregnancies included. Exposure to HPTs (n=227, 1.1%); exposure to control non-hormonal pregnancy test (n=876 biologic HCG tests, 4.4% or immunochemical HCG urine test n=415, 2.1%); 17,057 pregnancies with no test | HPT mainly composed of norethindrone or norethynodrel and estradiol or mestranol.

% of women exposed to test during first trimester: 93.4% HPT vs 80.6% serum HCG vs 82.7% urine HCG. | Re-evaluation of the association by other study designs of possible teratogenic effect of E/P used as HPT. | Anomalies (structural, functional, metabolic, chromosomal) ascertained at birth and in the years following, categorised as serious or not. | Rate of fetal death higher for all pregnancy test (PT) groups compared with non-test.

Crude rates of serious anomalies: HPT 4.4% (n=9) vs serum HCG 4.4% (n=30) vs urine HCG 2.7% (n=9) vs no test 3.8% (n=640) | Adjusted RR HPT vs serum 1.01 (0.47-2.19); HPT vs urine RR 1.60 (0.60-4.18)

No clustering of malformations by category. | Higher rate of death in all PT groups vs controls justifies the use of non-hormonal PT (rather than no PT) exposure as controls.

Findings do not support the hypothesis that E/P HPTs are associated with an excess of severe congenital abnormalities; however the numbers involved are not large enough to definitively reject the hypothesis either. | Specific for HPT. Comparison groups were equally assessed for birth defects and E/P exposure. Used LMP to determine gestational age. Optimal choice of controls - eliminates indication bias. Serum PT used 1959-64, supplemented by HPT in 1962, both supplanted by urine test in 1965. Thus exposed HPT group slightly different calendar time than controls. Adjustment for calendar year should have been done? Exposure to HPTs earlier in pregnancy than the other tests – indicator of different use/maternal risk factors? Women exposed to any PT had greater fetal loss, age over 40 and low birth weight. Small number of cases |
| Michaelis 1983 | Prospective cohort. Pregnant women seen within the first trimester of pregnancy asked to take part - 21 Obstetrics Depts in association with Children's Hospitals Germany, 1964-1972 | Women examined initially then observed once monthly. Particular attention to drug intake plus a number of other factors – recorded in diaries, also checked monthly. Children examined immediately after birth, days 3-5, 6wks, 40wks, 18 months and 36 months. All malformations checked by expert committee on human genetics and paediatricians. Records of intercurrent illnesses kept plus maternal concerns about development. Up to 4500 items recorded for each pregnancy. | NETA/EE – Duogynon

13,643 pregnancies total – 7870 in part I and 5773 in part II.
Controls matched according to Pat of study, hospital, maternal age, number of previous pregnancies and abortions and marital status.
610 matched pairs | To test the hypothesis for an association between HPTs (and antiemetics) and teratogenic effects | | 661 exposed pregnancies during first 12 weeks post LMP (341 (4.3%) in Part I and 320 in Part II (5.5%))
Most frequently taken during weeks 5-6 post LMP; earlier in 28 cases.
Additional sex hormones given in 114 (17.2%) cases. | 12 (1.8%) major malformations in exposed group.
OR 1.22 (0.53-2.94) in HPT vs control p=0.41) | Women taking NETA/EE tended to have more psychological stress and partner problems before pregnancy; shorter duration of pregnancy, greater unintended pregnancy (20% vs 7%) suggesting many unwanted pregnancies about HPT users. Overrepresentation of women with previous gestational complications and higher social class. HPT not significantly associated with an increase of major malformations. However, the upper 90% confidence intervals were rather high which could be regarded as being consistent with the positive findings of other studies and the lack of statistical significance interpreted as due to the small number of cases. | Rigorous prospective data collection, recruiting period mainly in first trimester (compared to study by Heinonen et al in which women were also included if first seen immediately before delivery). No obvious association but numbers too small to draw any firm conclusions. |

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Wiseman 1984	Re-analysis of base data from Heinonen study by analysis of original records.	Re-examination of records of all 19 cases hormone exposed with cardiac malformations and 100 of the 1023 exposed cases without cardiac malformations.		To examine three issues in particular – i) timing of administration, ii) incidence of serious maternal bleeding, iii) malformations in previous pregnancies	Maternal bleeding was not well defined in the original dataset.	No hormone given in 2 cases and 12 of the 100 controls; in 5 cases hormones were given too late for cardiac defects (between d19 and d50) Normals: 36 of 88 who received hormones started on treatment after day 50, 2 cases received hormones too early, 13 of 88 normals had hormones too early and 2 cases had Down's syndrome. 8 mothers received hormone during critical period vs. 38 exposed in normals Vaginal bleeding: 9 mothers of cases and 35 mothers of controls – difference not sig;	Previous pregnancies having minor malformations 12% vs 2%; major 17% vs 4%; stillbirths 6% vs 2%. 2 cases may not have had congenital cardiac abnormalities but transient functional murmurs.	Found a number of inconsistencies in the original base data. Incidence of exposure to sex hormones during the critical period was not significantly different statistically in those women whose children had cardiac lesions as compared with those without. Re-examination of base data of Boston CPP does not support the reported association between exposure to female sex hormones during pregnancy and the occurrence of serious cardiac malformations.	Schering employees. Individual patient files read by at least one author and up to 3 for controversial issues. Careful evaluation of the three main issues – no RR provided (Acknowledged that wasn't the main aim of re-evaluation).
Horowitz 1985	Analysis of epidemiological methodologies	Regardless of design, valid conclusions about causal associations require that the gps exposed to the drug under comparison have similar susceptibilities to the outcome at baseline. Matching or stratifying according to baseline demographics is the most common way to adjust for such differences. Noting what the drug was prescribed for is another good adjustor. Without knowing this it is impossible to know if the ordering of the HPT was a reflection of a clinical condition that increased the mother's likelihood of having a deformed child.		To examine the role of susceptibility bias in epidemiological studies of effects of pharmaceutical agents				The recognition and management of susceptibility bias requires attention to the patient's clinical status at the time of exposure to the alleged causative agent. Torf's presented data that strongly support the importance of susceptibility bias as an explanation for some of the false positive associations between sex steroids and birth defects whereas criticism of study by Nora et al – without evidence that women receiving hormones were clinically similar to those did not receive hormones the comparison can be seriously biased.	Importance of susceptibility bias – possible reference to confounding by indication i.e. individuals who are prescribed a medication or who take a given medication are inherently different from those who do not take the drug, because they are taking the drug for a reason

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Katz 1985	Historic prospective cohort	All patients (35,114) who delivered at Kaplan Hospital 1970-1979 were screened and only those who bled in first trimester of pregnancy were admitted (n=2754) . Bleeding (exact time of start and duration) identified through antepartum chart; name and dose of progestogen time of start and duration. Women treated by two sets of physicians who gave P (n=1608) or those who did not (n=1146). Those in the second group were controls to the first. Women similar with respect to baseline characteristics (maternal age, mean parity, incidence of maternal disease), distribution of the week in which bleeding started, interfamilial marriage, obstetric history, no malformations in previous studies, previous infants weighing <2000g or mean neonatal weight.	Progestogens: oral MPA 20mg/d; 17 hydroxy-progesterone 30mg/d. Mean duration of exposure 48 days	To determine the possible teratogenic effects of progestogens given in the first trimester of pregnancy.	Major mal-formation	Incidence per 1000 2.4 vs 4.4 for CNS; 53% vs 56% for bone and joint; but 4.3 vs 9.5 for cardiac defects. Overall defects 63 vs 72 per 1000 exposed vs control NS		No evidence of congenital malformation in women exposed to P.	By including only women who bled trying to reduce bias. Many risk factors were looked at and except for presence or absence of progestational medication during pregnancy the 2 groups of patients were comparable. OC use of conception not queried (from Poledak 85) No HPT included only supportive P therapy.
Polednak 1985	Critical review of evidence for an association between hormonal exposure in pregnancy and birth defects.							Little evidence for major, direct teratogenic effects of exogenous sex hormones. However there is evidence for slightly increased risks for certain defects including cardiac (perhaps 1.5-2 fold increase but paucity of data from prospective studies prohibit firm conclusions regarding causation), limb-reduction (association with HPT could be confounded by vaginal bleeding as bleeding has been associated with such defects), and multiple defects. Information on association between maternal sex hormone exposure and NTDs is limited. Further investigation is warranted for oral clefts and clubfoot.	

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Resseguie 1985	Medical records of 24,000 women who received prenatal care at the Mayo Clinic were reviewed to identify those exposed to sex hormones before birth (live and stillborn) 1936-1974.	988 cases exposed in utero to any exogenous progestin but no other sex hormone or gonadotropin. Controls matched 2:1 by sex, age number of live births and no exposure. Medical records abstracted by one investigator. Manually searched for anomalies and malignancies by investigator blinded to exposure.	Largely 17 hydroxy-progesterone (>60%) and progesterone; 11 NETA	To determine whether these is an increased risk of congenital anomalies among foetuses exposed to progestins in the absence of any other hormones		Higher rate of bleeding during pregnancy and prior fetal and neonatal deaths in exposed cohort. No tendency for excess of CV (0.9% vs 0.9%), CNS (2.5% vs 2.3%) or limb reduction anomalies (0.1% vs. 0.2%) or hypospadias observed in exposed group vs unexposed group.		No support for concept that progestins cause anomalies when given exogenously to pregnant women.	Examines progestogens only. Exposure occurred throughout whole of pregnancy, often with more occurring later. 75% exposure during 1st trimester. No information on indication. As records are so old they are likely to be less complete than current standards. Cox regression results not presented.
Lammer 1986	Retrospective case control in women registered to Metropolitan Atlanta Congenital Defects Program (MACDP), a population-based birth defects registry that began in 1968 and encompasses five counties with approx. 24,000 resident births per year.	Infants born between 1970-1979 included – total of 224,730 births. Mothers of malformed babies interviewed between 6-12 months post birth using standard questionnaire. Exposure was to exogenous sex hormones within the first 11 weeks of estimated date of conception. First trimester exposure for a particular malformation was compared with all others.	Progestogen: MPA, hydroxyl-progesterone and non-specified progestogens E+P: pill, HPT, supportive therapy	To evaluate the risk for a number of major mal-formations from exposure to exogenous female sex hormones, including HPTs.	Major congenital malformations	79% of cohort interviewed. 1091 malformations of which 136 (12.5%) reported first trimester exposure and 76 (7%) reported HPT use.	Of the 12 defect categories analysed only oesophageal atresia had a significant association with exposure (OR 2.84, 1.51-5.33, n=10 of 36) – no potentially confounding factors. Limb defects also showed sig association for HPTs (12 of 98 [12%] vs 58 of 957 [6%], OR 2.16, 1.24-3.76).	Found an association between oesophageal atresia and HPTs but findings do not clearly show that association is causal - absolute risk, if assuming causal association, low ~6 per 10,000 exposed live births.	In an effort to reduce maternal recall bias, this design would not enable a risk to be identified if sex hormones increase the risk of all malformations. Study had power to detect: NTD with OR of 2; 70% chance of limb reduction defects with RR 2. Authors suggest association likely due to chance because of the large number of analyses done. Large number of statistical tests done – possibility of association being random.
Hendrickx 1987	After confirmation of pregnancy 43 rhesus monkeys, 40 baboons and 61 cynomolgus monkeys were randomly split into groups then given control, 1x, 10x or 100x HDE of NETA/EE (for rhesus monkeys and baboons) or 100x, 300x and 1000x HDE for cynomolgus monkeys daily from day 20 – 50 of gestation. Fetuses delivered by CS at d100.		NETA/EE human dose 0.2mg/kg + 0.0004 mg/kg	To determine embryo-toxicity of E+P during early pregnancy in non-human primates.			Critical dosage level for embryolethality in all 3 species is 100X HDE. No malformations were observed in the rhesus monkey or baboon but skeletal (scoliosis) or genital malformations were observed in the cynomolgus monkey from doses of 100x HDE. The scoliosis was considered to be a spontaneous occurrence as it was an isolated case. Overall incidence of defects was 1.3% (2 of 152) equivalent to incidence of spontaneous defects.	Combined sex steroids such as those used in OCs and HPTs may be embryolethal at high doses but the effects of inadvertent exposure on surviving offspring are inconsequential.	

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Bracken 1990	Review and meta-analysis of prospective studies		OCs	to assess the typical relative risk from all the prospective studies of OCs and congenital mal-formations	Congenital mal-formations in stillbirths and livebirths		RR = 0.99 (95%CI 0.83,1.19)	Provides strong evidence against an association	Doesn't include HPTs so not relevant to this review. However a few points could be applied: in CC studies a variety of control groups are used hence sometimes difficult to compare, recall bias a big issue. Cohort studies – differential misclassification can occur especially because of a more intensive diagnostic search for malformations in diagnoses neonates. Also statistical power in detecting rare malformations (+ low exposure to the hormones) Also earlier studies show highest RR whereas recent ones have risks close to unity – tendency for earlier positive studies to be published?
Martinez-Frias 1998	Ongoing hospital-based case control from Spanish Collaborative Study of Congenital Malformations – including over 70 collaborating hospitals throughout Spain between 1976 - 1995.	20,388 liveborn malformed cases and 19,981 controls – next non-malformed infant of the same sex born in the same hospital as the case and from which same data was collected. Mothers questioned using defined protocols, including questions about 12 categories of drugs. Exposure was limited to any moment during the first trimester.	OCs E P E+P	The effect of prenatal exposure to sex hormones on congenital anomalies	600 different major and/or mild mal-formations identified within 3 days of birth	684 exposed cases (3.3%) 552 exposed controls (2.8%)	Cases had more vaginal bleeding, more prior abortions, more fertility issues and substantially more family history of malformations than controls. Cleft lip and palate were associated with exposure to OCs and P but the association became non-significant when results were stratified by the above mentioned confounding factors.	After controlling for potential confounding factors the results do not support the hypothesis that prenatal exposure to sex hormones increases the risk of genital and non-genital malformations.	Only includes malformations identified within 3 days of birth so incidence may be lower than in other studies however relative risks shouldn't be affected. Also only included livebirths. Limited to OCs and E, P and E+P but gives no information on indications for E, P and E+P if not for contraception. Exposure defined as the first trimester of pregnancy but this includes a substantial time when fetus is not susceptible to teratogenic effects (eg first two weeks and last 4-5 weeks)Multiple testing bias (although acknowledged and fewer statistical significance associations than those expected by chance) Rather than matching of cases and controls results were stratified by potential confounding factors.

Author (date)	Study design	Subjects/ participants (n)	Product	Objective	Primary outcome measure	N (events per exposed cases)	Results RR/OR	Authors' conclusions	Assessor comments
Hemminki 1999	Retrospective cohort in Helsinki, Finland	Women attending maternity centres in Helsinki between 1954 and 1963. 2052 exposed women - using E+/-P drugs. 2038 controls - next mother in file who had given birth during the same year and not prescribed hormones. Data on malformations extracted from maternity cards based on notes made by midwife based on hospital discharge summary. Exposure classified as any time in first 16 weeks.	Drugs containing oestrogen and or progestogen used most commonly for threatened abortion (47%), recurrent miscarriage (9%) and threatened premature birth (7%)	To study the effect of exposure to female sex hormones during pregnancy on mal-formation and cancer	Major and minor mal-formations; cancers in mothers and children	76 vs 40 malformations (including genital, major, minor and other severity unknown) P<0.001	No increase in cancer risk in mothers or children. Total number of malformations higher in exposed.	Supports hypothesis that E or P causes malformations in children exposed in utero but does not support causing cancer in mothers; power to study cancer in offspring very low.	Indication accounted for in only 63% of women. None states to be for HPT. Not clear how well recorded confounding factors, exposures, timing of exposures would have been made on the maternity cards so long ago, particularly as this was conducted retrospectively. But, does avoid recall bias. Not all confounding factors considered. Many outcomes based on very small (<10) numbers of cases. It is not clear whether data abstractors for malformations were blinded to exposure status but unlikely as outcome and exposure information all on maternity card. 16 weeks exposure includes much non-critical time. Although this study claims to support the hypothesis for an association between sex hormones and malformations the input data are not sufficiently reliable and the numbers are too small to be meaningful.
Tümmler 2013 Reprod Toxicol. 2014 Jan 2;45C:14-19. doi: 10.1016/j. reprotox.2 013.12.00 7. [Epub ahead of print	Retrospective case series: ADR reports made to BfArM by patients (primary source) or a self-nominated patient advocate (secondary source). Exposure between 1957 and 1981. Live born infants with congenital malformations claiming to have been exposed to Duogynon during pregnancy plus fetal deaths and pregnancy terminations with documented fetopathology. Major defects only coded.	Cases: Information from 78 primary subjects using standardised questionnaire. Info collected on dose, indication, time and type of application, maternal age, medical history, family history, exposure to other drugs, complications during pregnancy, pregnancy losses, gestational age at birth, sex, birth weight, length, head circumference and developmental disorders. 333 reports from the secondary source – no further info collected. Controls: All malformations occurring in the Malformation Monitoring Centre Saxony-Anhalt population based birth defect registry (started in 1980) between 1980 and 1989 – 3,676 out of 171,660 births..	Duogynon Oral NETA/EE (10mg/0.02 mg) IM 50mg progesterone + 3mg estradiol benzoate	To evaluate the contribution of the cumulative database of individuals potentially affected by Duogynon to the question of its teratogenicity	PRR for each mal-formation relative to all others	296 case reports in exposed and 3676 in unexposed (2%). Primary source cases: HPT as indication 79.4% Oral HPT 88% Secondary source: Duogynon confirmed as HPT in 11% of cases only	Primary source: 57% isolated defect; 41% multiple defects. Secondary source: 70% isolated and 20% multiple Most common defects: Skeletal system (43% and 39%) Urinary tract/kidney: 24% and 17%) Heart (23% and 12%) Bladder exstrophies most strikingly disproportionate in exposed OR 37 (14.6-95.3) followed by NTD (OR 3, 1.9-4.5), cleft lip and palate (OR 1.6, 1.1-2.4), skeleton (2.0, 1.5-2.5) and renal agenesis (OR 2.5, 1.2-5.5).	Bladder exstrophy caused by absence of mesodermal differentiation between 6th and 7th gestational week. However it is unlikely that such a substantial risk would have remained unnoticed in other studies. No decrease in bladder exstrophy could be demonstrated after withdrawal of HPTs. Excess risk of bladder exstrophy could be due to information bias. Underlying teratogenic effect is questionable in view of the methodological limitations and negative outcomes of other outcome studies in pregnancy post exposure to sex hormones.	No clinical verification of information provided by primary sources. Information collected decades after the event. All subjects have already decided that the drug was responsible for their defects therefore subject to extreme recall bias. Sparse information on all cases but particularly secondary source cases. Likely bias with secondary source reports in particular as the self-appointed advocate had exstrophy of the bladder and there has been much media interest in the case. Exact timing of administration known in only 7 primary source cases. All represent stimulated reporting. Controls and cases did not overlap in time because of the need to have controls in a period when Duogynon was not marketed, and information collected by completely different means hence the cases and controls not alike. Minor anomalies counted in exposed cohort but excluded in control group.