TERATOLOGICAL ADVERSE DRUG EFFECTS : REVIEW OF EVIDENCE IMPLICATING HORMONAL PREGNANCY TESTS.

Report to:

Sir Roland Moyle,
Minister of State,
Department of Health and
Social Services

and to:

Jack Ashley,Esq.,C.H.
Member of Parliament,
House of Commons

by Isabel Gal, MD.

C O N T E N T S

I N T R O D U C T I O N

"Don't use drugs if you
don't have to."
(Dr.Austin Flint,19th Century).

Historical background.

This long established medical principle has an added importance in pregnancy; as a rule no drug should be prescribed in early pregnancy without carefully weighing up the possible risk to the fetus.

Still the administration of massive doses of sex hormones,merely for diagnostic purposes, continued even after evidence showed the harmful effect of this unnecessary in-vivo method of pregnancy testing.

The unfavourable effect of synthetic sex hormones on animal reproduction was known long before the introduction of HPT products in 1958. Despite this, the manufacturers recommended HPT products as a safe and reliable method of pregnancy diagnosis and gave assurance that it does not interfere with the physiological course of pregnancy.

However, evidence gradually accumulated that these tests can disturb pregnancy because in a proportion of cases bleeding and abortions were observed following the HPT (Dienz-Risse 1956, Higgins-Sandler 1960).

The manufacturers assessment was not extended to the safety of developing fetus. This problem was raised, although in theory, soon after the introduction of HPT preparations (Edwards 1958), and in 1962 Dubowitz reported a single case already indicating the harmful effect.

The first conclusive evidence on the teratological effect of HPT was reported in a representative number in 1967 (Gal et al). It seems relevant to mention that at that time it was neither realised by the members of CSM nor by myself that doubt had been expressed on HPT products at an earlier date by the above workers. The manufacturers, most likely familiar with the above-mentioned concerns, failed to reveal these facts.

Manufacturers measures and effects.

Following the report in 1967 on the serious adverse effect of HPT, the manufacturers instead of withdrawing products with doubtful safety, introduced various measures (which later proved to be more safeguarding to themselves than the public). These measures varied by products and even by the same product in different countries, as their action apparently was influenced by the Authorities' attitude to the problem.

In the following the measures undertaken in Great Britain will be briefly outlined, where from the available 12 types of products suitable for pregnancy testing 7 were used for that purpose. HPT products were also recommended for the treatment of gynaecological disorders.

Measures undertaken by the Manufacturers
on HPT products at various years:

Product	Mfr.	1967	1968	1969	1970	1971	1972	1973	1974	1975	1976	1977	1978
Amenorone Forte	Roussel	T	T	T	x	x	x	x	x	x	x	W/MAY.	
Pregornot	Marshall			T	T	T	T						
Primodos	Schering	T	T	TØ	TØ	x	x	x	x	x	x	x	W/JAN.
Secrodyl	BDH	T	T	T	T	T	T	T	T	W/FEB.			
Disecron	Schering	T	T	W/MAR.									
Menstro-gen	Organon	T	T	T	x	x	x	x	x	W/MAR.			
Orase-cron	British Schering	T	T	T			x	x	x	W/JUNE.			

T: recommended for pregnancy testing

Ø: ceased promotion

x: changed indication

W: withdrawn/month

Blank: not available.

It emerges from the above that the manufacturers were recommending HPT products for many years after their adverse effect had been reported in 1967: even Pregornot was first introduced on the market two years later. Changes in promotion policy, or indication of these well introduced products did not alter their use for pregnancy testing.

According to the Medical Data Information the total prescription of HPT products and the rate of their use for pregnancy testing showed a steady increase after 1967.

	Total prescriptions: all purposes	For pregnancy testing
1968	1,212,000	15.1 %
1970	1,314,000	17. %
1971	1,202,000	19.4 %
1972	1,236,000	16.5 %
1973	1,036,000	11.5 %
1974	1,008,000	11.8 %
1975	371,000	12.8 %
1976	280,000	7 %
1977	306,000	2.3 %

The above suggests that medical practitioners were still using these products unaware of the hazard, because the manufacturers' measures were introduced inconspicuously without informing them. The unsatisfactory nature of these "preventive" measures has been repeatedly pointed out (Gal 1975, 1976).

On the other hand, it also indicates that after the DHSS issued warning notice in 1975, the use of HPT decreased remarkably, thus showing that medical practitioners are responding to yellow-warnings if issued.

Data obtained with the co-operation of
Oliver Gillie (Sunday Times).

DETAILS OF EVIDENCE ON HPT.

This review includes evidence on the teratological effect of sex hormones administered for diagnostic and occasionally for therapeutic purposes in early pregnancy. Studies investigating the direct or delayed effect of oral contraceptives are not included, as they represent a different problem (although related) and are beyond the scope of this review.

The commonly quoted references on HPT are listed below, in chronological order of publication, and grouped according to the investigator's own conclusions. The country of origin is also recorded to show the international interest towards the problem.

List of published evidence.

Studies reporting harmful effect

	Gal et al	Oct.1967	UK.
***	Crombie et al	Oct.1970	UK.
	Levy et al	Mar.1973	Canada
	Nora-Nora	Apr.1973	USA.
	Mulvihill et al	Sept.1974	USA.
	Janerich et al	Oct.1974	USA.
	Nora-Nora	Jan.1975	USA.
	Brogan	Jan.1975	Australia
	Harlap et al	Mar.1975	Israel
*	Greenberg et al	Apr.1975	UK.
**	Heinonen et al	Jan.1975	USA.
	Janerich et al	Apr.1977	USA.
**	Heinonen et al	Aug.1977	USA.
*	Greenberg et al	Oct.1977	UK.

Studies reporting trend of harmful effect.

Kullander-Källen	Jan.1976	Sweden
German Prospective Survey	June 1976	Germany

Case reports supporting harmful effect.

Dubowitz	Aug.1962	UK.
Kaufman	June 1973	USA.
Robertson-Rientoul	Aug.1974	Australia
Jaffe et al	Mar.1975	UK.
Dillon	Dec.1976	UK.
Roberts-West	Nov.1977	UK.

Studies refuting harmful effect

Smithells	Jan.1965	UK.
Laurence et al	Oct.1971	UK.
Oakley et al	Aug.1973	USA.
David O'Callaghan	June 1974	UK.
Goujard-Roquette	Feb.1977	France

List of unpublished evidence.

Studies supporting harmful effect.

RCGP Survey - Scotland	Jan.1969	UK.
*** RCGP Survey - England & Wales	Sept.1969	UK.
Roussel Laboratories	1969	?
Harlap-Davies	Jan.1978	Israel (reference in other publication)

Footnote:

Separate publications from the same survey:

* Preliminary and final reports (CSM own survey)

** Reporting one type of defect, and all types of defects (Heinonen et al).

*** Reporting stillbirths and all types of pathological conditions(RCGP).

Tabulated tables of available evidence.

The relevant details of the studies listed above are described on separate tabulated tables for reference and comparison purposes,(Tables i-vi) (Appendix A). In grouping the studies the investigator's own conclusions and the type of experimental methods applied were considered, Marked with serial number they are listed under the following main headings:-

Table I.

Studies reporting harmful effect (using healthy controls).

Table ii.

Studies reporting harmful effect (using controls with other birth defects).

Table iii.

Case reports supporting harmful effect.

Table iv.

Large-scale surveys.

Table v.

Studies refuting harmful effect (using healthy controls or incidence figures).

Table vi.

Study refuting harmful effect (using controls with other birth defects).

Remarks are made on each table on the studies themselves, and on the Authors'own conclusions.

German Research Association's Prospective Survey.

Detailed account of the relevant aspects of this survey are described separately (at Sir Roland's request) (Appendix B).

Summary of available evidence.

In this summary the available evidence are classified according to the Author's conclusion (comments to follow). Details of studies are on tabulated tables under appropriate serial number.

Evidence available before the issue of warning notice

Prior to the warning notice issued on 5 June 1975 by the CSM, the available evidence showed the following distribution:

5 confirming the harmful effect (P:value range between 0.001 - 0.05
Studies 1,2,3,4,5, (Table I)

12 confirming positive trend
Studies 9,10,11,12,13,14,15,16,19,20,21,27
(Tables ii,iii,iv)

4 excluding the harmful effect
Studies 28,29,30,31 (Tables v,vi)

Evidence available up to date.

These show the following distribution.

8 confirming harmful effect (P value range between 0.001 - 0.005
Studies 1,2,3,4,5,6,7,8 (Table I)

18 concluding positive trend
Studies 9,10,11,12,13,14,15,16,17,18,19
20,21,22,23,25,26,27 (Tables ii,iii,iv).

5 excluding harmful effect
Studies 24,28,29,30,31 (Tables iv,v,vi).

Statistical reassessment of studies.

Several different statistical methods were used in the evaluation of findings in studies on HPT and the Authors have expressed results either in percentages or the ratio between expected and observed figures, or in probability approximation. To show the problem in a more uniform pattern, statistical reassessment of studies were undertaken by:-

1. Fisher Exact Test (whenever it was possible): this is the most accurate analytical test as it expresses probability in exact figures and not in approximate as do the other probability tests. A computer program design for the Fisher Exact Test (B.Kelly) was used with the exception of large scale studies (Table iv) as they proved to be beyond the range of this particular program.
2. In these large scale studies the expected and observed figures were calculated; although this is not as accurate as the former test, it still was of assistance in establishing the trend.

Reassessment of studies having adequate controls were undertaken only. Groups without controls: (Smithells 1965, David O'Callaghan 1974, RCGP Survey 1969, Crombie et al 1970, Brogan 1975), or using other types of birth defects (Levy et al 1973, Mulvihill et al 1974, Nora-Nora 1975, Oakley et al 1973) were not investigated.

Results.

In all studies where Authors concluded positive findings (Studies 1,2, 3,4,5,6,7), (8 - under large scale studies), Fisher Exact Prpbability Test yielded significance at levels of:

Gal et al 1967	0.001
Nora-Nora 1973	0.0005
Janerich et al 1974	0.004
Harlap et al 1975	0.002
Greenberg et al 1975	0.004
Janerich et al 1976	0.0005
Greenberg et al 1977	0.001

In a study where the Author concluded negative finding (Study 29 Table v) while the non-significance was confirmed with the Fisher Exact Test, the deviation between expected and observed figures showed a positive distribution:

Laurence et al 1971	Fisher Exact:	0.326
	Expected :	20
	Observed :	22

In large scale surveys where Authors concluded positive trend (Studies 22, 23,25, Table iv) the deviation from expected figures were in positive direction:

Kallunder-Källen 1976	Expected :	18.75
	Observed :	21
German Prospective Survey 1977	Expected :	9.7
	Observed :	13
Heinonen et al 1977	Corresponding results with that of the Author.	

In a large scale survey where the Author concluded negative trend (Study 24, Table iv), the deviation from the expected figures was also in positive direction.

Goujard-Roquette 1977	Expected :	18.92
	Observed :	20

Conclusion of statistical reassessment:

From the 31 evidences (25 studies and 6 case reports) 12 studies proved suitable for statistical reassessment.

In studies where the Authors concluded positive findings, a significant correlation has been confirmed with the Fischer Exact Probability Test.

In the study where the Author declared negative results, the non-significant correlation has been confirmed with Fisher Exact Probability Test.

In this and in the remaining four studies, in all of which the Authors declared negative findings; without exception slight positive deviations were observed.

The uniform positive trend in all the above studies is relevant, even if the deviation is slight.

It would be unwise to dismiss the above facts.

Statistical review by:
B.Kelly,OBE.
Director of MRC
Computer Centre.

Estimated risks of damage caused by HPT.

There are several difficulties in establishing a straight relationship between the use of HPT products and incidence of birth defects, such as:

1. not every woman exposed to the test turned out to be pregnant,
2. HPT products are used for multi-purposes (e.g. diagnostic, abortificient and therapeutic).

On these grounds it is already obvious that neither the sales figures nor the prescription figures are sufficiently informative. Furthermore, HPT products used either for diagnostic or abortificient purposes, were often supplied by General Practitioners (from medical samples) or dispensed by chemists without prescription (Gal 1972/a).

Accurate data on the rate of abortions induced by the test are not available, Higgins-Sandler 1958, RCGP Survey 1969, Brotherton-Craft 1972, German Prospective Survey 1977, reported an increase between 7.5 - 24 per cent.

Maternal hormone treatment may also increase the rate of still-births. Crombie et al 1970 reported a double fold increase.

The available information on HPT relates to malformed live births only. Workers in USA. observed 2, 4, 4.5 and 8.5 folds increase (Heinonen et al 1977, Janerich 1974, Nora 1975 respectively). In Britain the estimated ratio of HPT affected cases amongst malformed live births were quoted 1.8 and 1.9 (Gal et al 1967, Greenberg et al 1977 respectively. The close agreement between these figures might suggest the average national incidence of HPT damaged live births in Britain (especially when one considers that these figures originate from different studies undertaken by different investigators at different times).

The above estimate relates to physical deformities only, but there are indications that HPT might induce other developmental anomalies, as reported by Goujard 1977, which issue requires further clarification.

Possible long delayed effect of HPT requires also consideration, because an association has been reported between maternal hormone treatment in early pregnancy and carcinomatous changes in adolescent children. During HPT, massive doses of sex hormones are administered at the critical stage of embryonic development; therefore its possible delayed effect also requires consideration. It has to be emphasised that such an association has not yet been reported in connection with HPT but in theory this is unfortunately not a remote possibility.

Authorities action on hormone pregnancy testing in Great Britain and abroad.

In the following countries the Authorities took action on HPT before any warning was issued in Great Britain.

HPT products banned.

Sweden	Nov.1970	National Medical Board
Finland	Feb.1971	National Medical Board

Warning notices issued:

Germany	1972	Federal Health Office
U.S.A.	Oct.1973	Federal Register
	Jan.1975	FDA.
Australia	Jan.1975	Federal Government
Ireland	Apr.1975	Drug Advisory Board
Holland	May 1975	Dept.of Health
Britain	5 June, 1975	Committee on Safety of Medicines.

Warning notices have been issued in many other countries since that time, even a reminder in some of them (including Britain in Nov.1977).

WHO.Actions on HPT.

Intergovernmental circular issued

1970 (No details). Information from: Nat.Med.Board of Finland.

11 Feb. 1975 No.1214	Requested by Health Authorities.	Australia
6 Apr. 1975 No. 150	Requested by FDA.	U.S.A.
22 July 1975 No. 155	Requested by Health Authority,	New Zealand.

The above circulars were also sent to CSM. Information from WHO.

Drug Information Bulletin Reports.

October 1977 PDT/D1/77.3	Hormonal exposure during pregnancy - the danger of birth defect.
October 1977 PDT/D1/77.3	Drugs and malformations - further evidence against hormonal pregnancy tests.

The above informations are most likely incomplete owing to the confidential nature of Authorities undertakings.

It still illustrates that preventive measures on HPT were introduced earlier in many parts of the World than in Britain, in spite of the fact that the CSM was the first medical Authority to know of this hazard.

The above also illustrates the appreciation of the possible teratological risks of HPT by the other Authorities.

Data obtained with the co-operation of
Oliver Gillie (Sunday Times).

Views and actions of CSM on HPT.

There seems to be a conflict between the Committee's views and actions concerning this matter. On 22 June 1967 the CSM (at the time the Committee on Safety of Drugs) concluded that the report they had received on the teratological adverse effect of HPT

1. Produced prima facia evidence that the abnormalities may be drug induced
2. The findings should be published so that the profession may be alerted to the possibility that these tests may be dangerous
3. It would not be a disaster if publication reduced the frequency of their use, as these drugs are used simply as conventional diagnostic tests
4. That the rights and wrongs of using these hormones for diagnostic purposes must be regarded as entirely separate issue from the scientific interpretation of a possible cause/effect relationship between test and congenital malformation.

(extract from CSM letter dated 23.6.67).

Nevertheless, instead of taking efficient action, the Committee decided to gather further evidence, and at their request the Royal College of General Practitioners investigated the problem. Within a relative short interval in January 1969, their preliminary findings substantiated the harmful effect of HPT.

The Committee knew about the outcome of this Survey and did nothing. In February 1969 they even turned down a request from Schering Chemicals(UK)Ltd. who sought help to pressurise the Parent Company in Berlin to agree to the withdrawal of their HPT products in Britain. (This approach by Scherings(UK)Ltd. to CSM in February 1969 was the second of its kind, the first being in mid 1968.)

It might be also relevant that the findings of the RCGP survey were neither published nor were any references made to them in any of the relevant publications of the Royal College of General Practitioners or the DHSS.

In the intervening years much evidence accumulated, but this still did not convince the Committee to take action, because meanwhile they themselves were investigating the problem and its possible outcome was awaited. However, when their preliminary findings substantiated the harmful effect of HPT. (Greenberg et al 28 Apr.1975), the Committee did not issue Warning Notice. This was done only on 5th June 1975, following the pressure of the public press (Sunday Times 25 May 1975).

On the delay in issuing the warning on HPT the Chairman of the Committee stated that "it was partly the result of scientific caution and partly the result of great caution in avoiding giving advice to doctors on medical practice without positive evidence (Sunday Times, 8 June 1975). By that time 17 evidences were available which either confirmed the association between HPT and birth defects showed a positive trend (Page 8.).

Ironically when the CMS own survey confirmed the observation (Greenberg et al 1977) the scientific aspect of the problem became the central issue, and an attempt is being now made to explain that much of the delay was due to criticism made of the publication in 1967 (these are discussed in the comments at the end of this review).

Instead of giving due recognition to the original discovery,the Minister of State repeatedly stated in Parliament (21 Nov.1977 and 26 May 1978), and also released to the public press (DHSS Press Communique) that the study which revealed a widely operating teratogen "is open to criticism on scientific grounds".

Apparently Medical Authorities abroad had different views about the same study, for example:-

The WHO stated "it brought into serious question the wider issue of the possible teratogenic potential of synthetic sex hormones, whether used diagnostically,therapeutically or inadvertently during early pregnancy" (Bulletin PDT/D1/77.3.1977).

The Netherlands Committee for the Evaluation of Medicine commented on the study "though the data were presented with restraint,they should even at that time have provided sufficient reason to review critically the further use of these tests" . Furthermore "... it is rather a horrifying thought that almost 10 years to the day after Gal's original paper, Greenberg, Inman et al found it necessary to report on a further series of malformed children whose mothers had taken hormonal pregnancy tests"(Side Effects of Drugs Annual, 2 1978).

Considering that the observation on the teratological effect of HPT was made soon after Thalidomide events,there seems to be no justification for not recognising the practical implications of the possible hazard by the Committee on Safety of Medicines. a Body set up for the very purpose of preventing the recurrence of similar events to Thalidomide tragedy.

Owing to the delay of introducing effective measures on HPT many women were exposed to an unnecessary hazard.

Comments on some of the scientific aspects of the problem.

The observation on the teratological effect of HPT has met with considerable opposition by scientists who were having influence on medical problems in Great Britain, and their attempt to suppress the issue possibly played a part in the endless criticism of studies indicating the harmful effect of HPT and the ready acceptance of less thorough investigations resulting in refuting findings.

In view of the recent references to the scientific criticism of the original observation made in 1967, these will be quoted and briefly discussed:

1. Method of selection of cases:
   commented by: CSM. 1967
   Laurence 1972.
2. Reliability of retrospective information
   commented by: Smithells 1967, 1976, 1978
3. Role of confounding factors
   commented by: Jeffcoate 1967.
4. Relevance of the stage of pregnancy at the time of the test
   commented by: Sever 1973
5. Type of induced malformation
   comment by: Inman 1975

Since then references are made, either one or a combination of the above, without questioning the acceptability of these comments, even by those who themselves have not used any of these criteria in their own study.

ad.1 The validity of the observation on HPT was questioned because it was discovered through restrospective information (Smithells 1967,1976,1978) While there is little doubt regarding the fallibility of information gathered reetrospectively, when causal events are investigated, as a rule important occasions are well remembered. Women usually have good recollection on the occasion when their pregnancy was diagnosed. In my study the information given by mothers corresponded with that of the medical practitioners.

Close observation of the outcome of HPT studies revealed that positive and negative results emerged both from retrospective and prospective studies, such as:-

Positive results : 8 prospective studies
12 retrospective studies

Negative studies : 2 prospective studies
3 retrospective studies

ad. 2. Method of selection of cases.

In the studies included in this review the index cases were drawn either from hospital patients or malformations registry, and from epidemiological types of surveys. In the selection of control cases even more variety may be noted, some of the studies used healthy or malformed control cases with or without HPT, whereas others used more refined experimental design and conducted a case-control study in which various matching criteria were applied. In the included 7 case-control studies, altogether 10 types of matching criteria were used in various numbers and combinations. From these criteria some workers placed value only to the catchment area where the cases selected were from (Inman 1967, 1975, Laurence 1972). The relevance of catchment area in relation to HPT is based on the possible variation in prescription habit of general practitioners. On this ground Roger-Weatherall 1976 anticipated clustering of malformations due to HPT.

Doubtless that the catchment area is an important issue, but in post-partum studies on HPT this question requires more consideration. It has to be realised that the place of conception does not always correspond with the area of birth (moving home is a frequent preparation for the arrival of a new baby). In my study : 4:19 index cases and 3:4 control cases had HPT. in different areas than where the delivery took place.

Noteworthy to mention that the rate of use of HPT in my study corresponded with the rate observed in two major surveys undertaken in England and Wales; in the control group with the Royal College of General Practitioners' Survey (Crombie 1974) and in the index group with the CSM's own survey (Greenberg et al 1977), thus suggesting that the rate of the HPT in my study revealed an average national incidence without matching the catchment areas.

(This issue has been personally clarified with the CSM, through Dr.Inman, in 1967, and again in 1975).

ad.3. Role of confounding factors

In assessing the teratogenic effect of a single agent with reasonable accuracy,other factors with possible similar effect should be excluded. To assess the possible masking effect of cause/effect relationship, cases with poor genetic background or reproductive history, or exposure to other unfavourable environmental factors,have been excluded in my survey(see Table I. Study 1) but it did not alter the result of the study (Gal 1972/a, 1972/b).

4-5. Stage of pregnancy at the time of the test, and the type of developing deformity - or deformities.

There are several difficulties to establish with accuracy the stage of pregnancy or the stage of embryonic development at the time of the test. In clinical practice the former is deduced from changes occurring in cyclic pattern and the embryonic developmental scales used at present for humans are extrapolated from information obtained from other species. Furthermore the mechanism of human maldevelopment is as yet not fully understood. Sever 1973 emphasised this issue.

That HPT does not produce characteristic malformation has been quoted to discredit its teratogenic properties (Inman 1975). As evidence on various types of deformities accumulated it was obvious that the harmful effect is not specific but depends on the stage of fetal development when the insult occurs (Gal 1977). This view has been accepted and reiterated (Greenberg et al 1977).

After the intake of HPT products a few more days are required for the biochemical changes to develop, on which the mode of action of the test is based. The duration of the activity of the drug in the body may vary from days or weeks, possibly depending on the strength of the product used, and on the host's own detoxicating capacity. This may explain the occurrence of wide range of malformations, and also the association of various anomalies developing at different stages of gestation. HPT products chemical composition is closely related - therefore the degree of their toxicity probably depends on the amount of hormones included in the tablets and on the total dose used during pregnancy testing.

In the initial report on HPT attention was also drawn to the possible similar influence of oral contraceptives if administered inadvertently in early pregnancy (Gal et al 1967) due to the fact that oral contraceptives and HPT products contain similar sex hormones, although in varying amount and combination.

The total intake of oestrogen and progestogen with various HPT products are shown on the following table: and for meaningful illustration it is related to the recommended daily intake of the same hormone derivates administered in the form of oral contraceptives either of low potency formulation (Minovlar) or of high potency formulation (Gynovlar).

Type of HPT. product	Total Oestrogen intake			Total Progestogen intake		
	Total/mg.	Equivalent comparison/days		Total/mg.	Equivalent comparison/days.	
		MINOVLAR	GYNOVLAR		MINOVLAR	GYNOVLAR
Amenorone	0.20 mg	4 days	4 days	200 mg	200 days	66 days
Amenorone Forte	0.15 mg	3 days	3 days	150 mg	150 days	50 days
Menstrogen	0.20 mg	4 days	4 days	200 mg	200 days	66 days
Orasecron	0.50 mg	10 days	10 days	100 mg	100 days	33 days
Progornet	0.15 mg	3 days	3 days	150 mg	150 days	50 days
Primodos	0.04 mg	< 1 day	< 1 day	20 mg	20 days	6 days
Socrodyl	0.20 mg	4 days	4 days	40 mg	40 days	13 days

The above table may illustrate that during HPT testing much higher doses of hormones are administered than hitherto believed, for example, the amount of Progestogen used in the course of pregnancy testing with Amenorone Forte or Menstrogen (administered within 4 days) is equivalent to the amount used with Minovlar during 9 cycles,or with Gynovlar during 3 cycles.

Studies often failed to discriminate between HPT and oral contraceptives, and omitted the marked differences in their strength, and also the relation of their use to the stages of fetal development. Robinson 1971, RCGP Survey 1976, Heinonen et al 1977, Harlap-Davies 1978, in their study on oral contraceptives, evaluated separately the effect of inadvertent oral contraceptive therapy in early pregnancy, and their findings also indicated a trend of harmful effect.

The Royal College of General Practitioners' Survey in Scotland (1969) revealed a higher incidence of malformations following the use of Primodos and Secrodyl than with other types of popular HPT products used in Britain. It was assumed therefore that these preparations are more toxic than the others (Gal 1972/a). As these tablets are having the lowest hormone concentrations within the range of HPT tablets, it is also possible that products with lower concentration tend to damage the fetus, while those having higher hormone content more often terminate pregnancy.

The above observations may alter the view that HPT products are only toxic in excess doses (Scherings Chemicals,Ltd. 1968)

While the clarification of the above would be of great scientific importance, it has to be emph asised that in the practical handling of the issue on HPT they are having little relevance.

CONCLUSION.

This review summarises evidence accumulated following the initial report on the teratogenic effect of HPT. It illustrates the tragic outcome of exposing women to unnecessary hazard, while those in a position to prevent it were searching for further evidence and hard and fast scientific proof.

From the available evidence it may be concluded that the teratogenic effect of HPT has been confirmed as far as this potential of substances can be proven in human subjects, with the types of investigations reviewed.

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SUMMARY

A literature search conducted to evaluate the teratological effect of sex hormones used in early pregnancy yielded 27 publications on this topic, of which 22 show either statistically significant increase in abnormality or a trend in the same direction. Statistical reassessment of the remaining studies also show a trend in this direction. In a small number of studies the methodology might be considered inappropriate.

4 unpublished surveys also revealed positive trend.

In 1971 - and 1972, the Authorities in Sweden and in Finland banned the sales of HPT products, and between 1971 - 1975 five further countries have issued warning notices; all prior to that from the DHSS. During the same interval several inter-governmental circulars were issued on this topic by the WHO.

It is proposed that irrespective of discerning opinion, the weight of existing evidences are sufficient to justify:

a) placing the onus of proof of safety of HPT products on the manufacturers.

b) an earlier warning by the CSM.

These are considered especially relevant in HPT.products, as they were used for diagnostic purposes when alternative reliable diagnostic tests for pregnancy were available.

The above might also be considered to vindicate the observation made in 1967.

APPENDIX / A

TABLES I - VI.

STUDIES REPORTING HARMFUL EFFECT (using healthy controls).

TABLE II

Author and Serial No.	Type of Study	Type of Malformation investigated	Source of Material: Index	Source of Material: Control	Criteria of matching controls	Source of Information	Hormone treatment: Product Specified	Hormone treatment: Stage of pregnancy exposed in:	RESULTS: No. of cases: Index: Total	RESULTS: No. of cases: Index: HPT	RESULTS: No. of cases: Controls: Total	RESULTS: No. of cases: Controls: HPT	RESULTS: Expressed by Author.	RESULTS: Excluded Confounding factors.
Gal et al 1967 1.	Retrospective matched case-control	Spina-Bifida hydrocephalus	Hospital cases	From other hospital	Maternal age, Reproductive history: parity, abortions malformations Present pregnancy course Season of birth Sex of baby	Mother O.P. Midwife Hospital	Primodos Amenorone Forte	Weeks (ovulation age)	100	19	100	4	P < 0.001	Maternal Illnesses before/during pregnancy Drugs before/during preg. Past history of: Fertility ie, current Abortion, stillbirths, Malformed births.
Para-Nora 1973 2.	Retrospective	Heart	Hospital cases	-	-	-	-	Trimester	224	20	262	4	P < 0.001	-
Janerich et al. 1974 3.	Retrospective case-control	Limb	Malformation registry	-	-	Mother	"Oral and injection"	Trimester	108	15	108	4	P < 0.02	-
Kirlap et al 1975 4.	Prospective	All types	Cases from 11,468 Survey Malformed	Healthy	-	Mother	Partly specified	Months	432	47	11036	385	P < 0.002	-
Greenberg et al. 1975 5.	Retrospective matched case-control	All types	Malformation registry.	Same medical practice	Medical practice Season of birth	Medical Records	-	Trimester	149	23	149	8		Iron and folic-acid intake in pregnancy
Janerich et al. 1976 6.	Retrospective case control	Heart	Malformation registry	-	-	Mother	-	Trimester	104	18	104	3	P < 0.001	Iron and vitamin intake in pregnancy
Heinonen et al. 1977 7.	Prospective case control	Heart	Cases from 50,282 Malformed	Healthy	-	Mother Medical records	Oestrogen Progestogen alone or combination	Trimester	1042	19	50,282	404	P < 0.05	Past History of Abortion Stillbirth Malformation Pregnancy complications.
Greenberg et al. 1977 8.	Retrospective matched case control	All types	Malformation registry	Same medical practitioner	Medical practice Season of birth	Medical record	-	Trimester	836	93	836	55	P < 0.01	History of malformed births

REMARK

Greenberg et al 1975 and 1977 represent one study.

STUDIES REPORTING HARMFUL EFFECT
(using controls with other birth defects).

TABLE II

Author and Serial No.	Type of Study	Type of Malformation investigated	Source of Material: Index	Source of Material: Control	Criteria of Matching controls	Source of Information	Hormone treatment: Product Specified	Hormone treatment: Stage of pregnancy expressed in:	RESULTS: No. of cases: Index: Total	Index: HPT	Controls: Total	Controls: HPT	Expressed by Author	Excluded Confounding factors.
Levy et al 1973 9.	Retrospective matched control	Heart (TGV)	Hospital cases	Mendelian disorders	Season of birth	Mother	-	Weeks	76	7	76	-	P 0.007	-
Malvhill et al. 1974 10.	Retrospective	Heart(TGV)	Hospital cases	Other heart defect(septal)	-	Mother	-	Trimester	88	5	88	4		
Nora-Nora 1975 11.	Retrospective	Vacterl	Malformation registry	Healthy Mendelian anomaly	-	Mother	-	under 45 days	19	13	38	-		Drugs in pregnancy Malformation in the family.
Progon 1975 12.	Retrospective	Cleft lip Cleft palate	Malformations registry Cases with HPT	-	-	Medical records	Duogynon Amenorone Forte Nonstrogon Secrodyl	Weeks	220	20	-	-	10%	

REMARK:
Levy et al: relatively high proportion of index had therapeutic hormone treatment/no data on controls.

TABLE III

CASE REPORTS ILLUSTRATING POSITIVE EFFECTS

Dubowitz	1962	(1 case)	Virilication following Amenorone Forte
Kaufmann	1972	(1 case)	VACTERL syndrome, following combination of Stilboestrol oral and Progesterone I.M.
Robertson-Rintoul	1974	(4 cases)	Heart(2), Skeletal(1), Exencephalos(1), following Primodos and Minovlar.
Jaffe et al	1975	(6 cases)	Limb deformities, following sex hormone therapy (unspecified).
Dillon	1976	(14 cases)	Genito-urinary(4), Nervous System(3), Heart(5), Eye(1), Limb(1), following par specified hormone therapy.
Roberts-West	1977	(1 case)	Urinary tract, following Progestogen.

LARGE-SCALE SURVEYS

TABLE IV

Author and Period No.	Type of: Study	Type of: Malformed Investigated	Source of material: Index	Source of material: Control	Criteria of matching controls	Source of Information	Hormone treatment: Product specified	Hormone treatment: Stage of pregnancy expressed in:	RESULTS: No. of cases: Index Total	Index HPT	Controls Total	Controls HPT	Expressed by Author	Authors own comments
BCCP Survey England & Wales 1969 19.		All types abortions still-births	Cases from 10,000 survey With HPT.	-	-	Medical records	Primodos Amenorone F, Oranecron Socrodyl Others	-	411	31				Showing positive trend
BCCP Survey Scotland 1969 (unpublished) 20.									135	15				Crombie Personal Communication 1969 Kunsberg Personal Communication 1969
Crombie et al. 1970 21.		Malformed births	Cases from 10,000 survey With hormone treatment	-	-	Prescription	-	Under 9 weeks Over 9 wks.	not given				Expect. 8.3 Observ. 18	Highly significant
Zellender-Effen. 1976 22.	Prospective		Cases from 5753 survey Malformed with HPT. (Figures on malformation extracted)	Healthy with HPT.	-	Mother	Primodos	Months	745	20	4910	107	Expect. 2.2 Observ. 8	Figures do not exclude nor support teratogenic effect. A weak correlation between sex hormones and malformed births without any cause and effect.
German Prospective Study 1977 23.	Prospective	Heart Club Foot	Cases from 7870 survey Cong.heart with HPT.	Healthy with HPT.	-	Mother	Duogynon and others	Trimester	33	13	66	16	Control 24% Index 39%	Statistically not significant but showing trend. Similar comments on Club foot, without data.
Goujard-Rogelette 1977 24.	Prospective	Heart Skeletal Microcephaly	Cases from 9822 survey Malformed	Healthy	-	Mother	Testosterone Progesterone	Trimester	160	20	9662	11451	Inc/Nat.incidence/1000 4.2-4 Heart 4.2-5.2 Skeletal 3.2-0.6 Microcephaly.	No definite evidence, risk small for malformation. Significancy of microcephaly, difficult to interpret.
Heinonen et al. 1977	Prospective	All types	Cases from 56,282 survey .with hormone treatment				1.Progestetional Total 866 Malf. 47		Expected 45.4 Observed 47	Heart 8.9 16.				Overall association limited. Risks of cardio-vascular malformations significant (double) Risks increase in certain minor defects (e.g. hypospadiasis)
							2.Progesterone Total 253 Malf. 9		Expected 12.3 Observed 9					
							3.Oestrogenic Total 614 Malf. 35		Expected 32.3 Observed 35	Heart 6.3 12.				
							4.Diethylstilbestrol							

STUDIES REFUTING HARMFUL EFFECT
(using healthy controls or incidence figures).

TABLE V

Author and Serial No.	Type of Study	Type of Malformation investigated	Source of Material: Index	Source of Material: Control	Criteria of matching controls	Source of Information	Hormone treatment: Product Specified	Hormone treatment: Stage of pregnancy expressed in:	RESULTS: No. of cases: Index Total	Index HPT	Controls Total	Controls HPT	RESULTS: Expressed by Author	Authors own comments
Smithells 1965 28.	Prospective	Heart	Malformation related to prescription record	registry	-	As material	Amenorone	Days, weeks	189	3			No evidence	Small group provides no evidence.
Laurence et al.1971 29.	Retrospective matched case control. (3 parts)	Spina-Bifida anencephaly	Unspecified	1.Hospital 2.Hospital 3. -	Parts: 1.Area, season of birth 2.Area, parity season of conception 3.Previous malformed sibs.	-	-	- -	271	22	323	22	Index Expected 20 Observed 22 Control Expect 23.9 Observ. 22	No significant association
David O'Callaghan 1974 30.	Retrospective:	Oesophageal Atresia	incidence figs of malformation(1 type)	Sales figures of 3 types HPT products	-	International Marketing Service & Manufacturers		- -	-	-	-	-	linear correlation not detected.	Data does not support association.

REMARKS

Smithells 1967, David O'Callaghan, Laurence et al } Data not sufficiently reliable

Showed positive deviation from the expected figure.

TABLE VI

STUDY REFUTING HARMFUL EFFECT,
(using controls with other birth defects).

Oakley et al 1973 31.	Retrospective	All types	Malformed with HPT	Chromosomal anomaly with HPT	-	Mother	"oral and injection"	- -	361	40	72	6	Index 11.1% Control 8.3%	The use of HPT in 10.6% of malformed cases (46/433); no definite evidence to support nor to exclude the teratogenic effect.

A P P E N D I X / B

GERMAN PROSPECTIVE STUDY

prospective study 1977 [33]		Club Foot	Cong.heart with HPT.	Healthy with HPT.	-	Mother	Duogynon and others	Trimester	33	13	66	16	Control 24 Index 39	Statistically not significant but showing trend. Similar comments on Club foot, without data.
Goujard-Briquetto 1977 [24]	Prospective	Heart Skeletal Microcephaly	Cases from 9822 survey Malformed	Healthy	-	Mother	Testosterone Progesterone	Trimester	160	20	9662	11451	Inc/Nat.inc-idence/1000 4.2-4 Heart 4.2-5.2 Skeletal 3.2-0.6 Microcephaly.	No definite evidence, risk small for malformation. Significancy of microcephaly, difficult to interpret.
Heinonen et al. 1977 [25]	Prospective	All types	Cases from 56,282 survey with hormone treatment				1.Progestational Total 866 Malf. 47	Expected 45.4 Observed 47	Heart 8.9 16.					Overall association limited. Risks of cardiovascular malformations significant (double) Risks increase in certain minor defects (e.g. hypospadiasis)
							2.Progesterone Total 253 Malf. 9	Expected 12.3 Observed 9						
							3.Oestrogenic Total 614 Malf. 35	Expected 32.3 Observed 35	Heart 6.3 12.					
							4.Diethylstilboestrol Total 164 Malf. 12	Expected 1.04 Observed 12.						
Kirlap-Dorien 1978 [26]	Retrospective	All types	HPT. cases from 16,583 survey				No details, reference in relevant publication Chap.3 p.77							Excess of malformations observed in association with pregnancy test. To be reported elsewhere.
Brussel Survey 1969 (unpublished) [27]							No details.							"Preliminary evaluation: Highly significant findings". Reference in Schering Documents 1969.

Further:

Hallunder-Mellon 1976 — Expected figure 18.75 observed 22.

Jerusalem Prospective Study 1977 — Expected figure 9.7 observed 13

Goujard-Briquette 1977 — Expected figure 18.92 Microcephaly P = 0.01 observed 20

Heinonen et al. — Expected and observed figures as above (Details on heart defects on Table I.)

R.C.G.P.(unpublished)
England & Wales — (Independent statistician concluded
Scotland — (significant association.

APPENDIX B.

Extract from Prospective Survey of the German Research Association on the effect of synthetic sex hormones in early pregnancy.

The outcome of 14,800 pregnancies has been investigated in this comprehensive survey. The preliminary report (June 1977) refers to (7,800) cases.

The effect of Duogynon (the German trade name of Primodos) and other sex-hormone products was included in the investigation. The immediate and delayed effects of the use of these products was evaluated from the following aspects:

(a) Attempted abortion (page 29, para. 2)
The rate of abortion was found to increase from 2.2% to 8.6% after Duogynon administration.

(b) Bleeding (pages 30 and 35, last par. on both)
After Duogynon treatment the rate of bleeding was found to be 24.8%. This ratio was found to be equal both in wanted and unwanted pregnancies.

Consequences of bleeding were recorded to increased rate of:-

Prematurity	from	6.6%	to	12.8%
Mortality	"	2.1%	"	4.6%
Other damage	"	0.7%	"	2.0%

In consideration of the above, the report concluded that the use of Duogynon is most likely not without consequences on the fetus (page 29, para.2.)

(c) Congenital malformations. (Page 56, paras, 3-4)
The analysis extended to club-foot and heart defects only (reference to other malformations was not reported in connection with HPT.)

A correlation between the incidence of club foot and maternal hormone treatment has been referred to but without giving figures on which the observation was made.

The report gives more information on the association of HPT and heart defects.Besides Duogynon the use of other hormone preparations were also recorded. The survey revealed that out of 33 malformed cases,13 were exposed(39%),and out of 66 healthy controls 16 were exposed(24%) to hormone therapy. The report

concluded that the 15% difference between the index and control group is indicative of a trend, but it requires further clarification (page 57,para 1.)

The discussed pathological changes,in my opinion, provide support rather than refute evidence regarding the harmful effect of sex-hormones used in early pregnancy.