Annex E. Hormonal Pregnancy Tests Supporting Information

Contents

Introduction

HPT products marketed in the UK

1. From the 1950s to the 1970s hormonal pregnancy tests were used in the United Kingdom. The most commonly used product was Primodos, but various brands and formulations were available, see Table E.1 Availability of HPTs on the UK market. This table is taken from the 2017 EWG Report. taken from the Report of the Commission on Human Medicines Expert Working Group Report 2017.[1] These products generally consisted of a combination of an estrogen (usually ethinyliestradiol or EE) and a progestogen, some HPTs, for example Norone, consisted of just a progestogen (norethisterone NE).

Hormone(s)	Products	Dates available in UK
Ethinylestradiol and ethisterone	Amenorone	1950 to 1977
	Amenorone Forte	Until 1977**
	Disecron	Pre-1952* to 1969
	Menstrogen	1951 to 1975
	Orasecron	1950 to 1975
	Paralut tablets	NA
	Paralut Forte tablets	NA
	Pregornot	Pre-1970* to 1973
Ethinylestradiol and norethisterone acetate	Norlestrin	1961 to 1975
	Norlutin-A	1961 to 1975
	Primodos oral	1958 to 1978
Ethinylestradiol and dimethisterone	Secrodyl	1961 to 1975
Estradiol benzoate and progesterone	Paralut injection	NA
	Paralut Forte injection	NA
	Primodos injectable	NA
Norethisterone	Norone	1965 to 1969

Table E.1 Availability of HPTs on the UK market. This table is taken from the 2017 EWG Report.

NA information not available * exact date not known **withdrawal date only known

[1] Report of the Commission on Human Medicines Expert Working Group on Hormone Pregnancy Tests 15 November 2017 available at https://www.gov.uk/government/publications/report-of-the-commission-on-human-medicines-expert-working-group-on-hormone-pregnancy-tests

2. The formulations and dosages of the HPTs varied between brands and within brand over time. Primodos, the most commonly used product, contained 10 mg per tablet of the progestogen norethisterone acetate (NE) and 0.02 mg per tablet of the synthetic estrogen ethinylestradiol (EE) in a single tablet.[2] One tablet was taken daily for two consecutive days. If the woman was not pregnant a withdrawal bleed followed up to a few days later. In pregnant women there was no withdrawal bleed.[3]

3. A paper from 1960 written by two GPs[4] describes their understanding of the way hormone pregnancy tests work as *'The two tablets are taken on each of two successive days. If the amenorrhoea is of psychosomatic origin, then bleeding resembling a normal period occurs within three to seven days. If the amenorrhoea is due to an early pregnancy no bleeding occurs, as the tablets augment the normal hormone production of the ovaries, so tending to protect the pregnancy.'*

Prevalence of HPT use

Numbers of women who took HPTs

4. This issue has been explored in section 2.3.3 of the EWG Report.[5] Unfortunately, there are several factors that make estimating HPT usage as a pregnancy test difficult.

Prescriptions

5. The available data (taken from Dr Wiseman's Report available at Annex 13 of the EWG Report) is known to be incomplete for several reasons. Data of GP prescriptions for HPT products is taken from the Medical Data Index (MDI); MDI figures do not include sales to hospitals or clinics under the Area Health Authority so underestimate actual sales. MDI data is unavailable pre-1966, see Table E.2 MDI and Sales data for Schering and Roussel HPT products from 1959-1979.

[2] These doses were from 1963 onwards. Primodos was reformulated on several occasions before this, see Annex 3 'Updated Chronology' of the Report of the Commission on Human Medicines Expert Working Group on Hormone Pregnancy Tests 15 November 2017 available at https://www.gov.uk/government/publications/report-of-the-commission-on-human-medicines-expert-working-group-on-hormone-pregnancy-tests

[3] We are aware that a proportion of women did bleed after using HPTs even though they were pregnancy.

[4] Higgins, GL and Sadler, WR 'A two-tablet oral pregnancy test' Practitioner 1960: **185,** 677-80

[5] Report of the Commission on Human Medicines Expert Working Group on Hormone Pregnancy Tests 15 November 2017 available at https://www.gov.uk/government/publications/report-of-the-commission-on-human-medicines-expert-working-group-on-hormone-pregnancy-tests

Sales figures

6. Roussel and Schering products held over 90% of the total HPT market share. Table E.2 MDI and Sales data for Schering and Roussel HPT products from 1959-1979Table E.2 MDI and Sales data for Schering and Roussel HPT products from 1959-1979 shows the official sales data from Roussel and Schering broadly agrees with the MDI prescription data. This sales data includes sales made for both pregnancy testing and treatment of secondary amenorrhea. This sales data also included the free samples distributed by Schering.

Year	MDI Prescriptions data (000s)	Actual Sales (000s)
1959		105
1960		178
1961		269
1962		307
1963		373
1964		405
1965		483
1966	475	516
1967	545	534
1968	490	523
1969	530	530
1970	560	581
1971	480	530
1972	455	490
1973	355	445
1974	360	361
1975	180	215
1976	110	134
1977	85	86
1978	10	0
1979	0	0

Table E.2 MDI and Sales data for Schering and Roussel HPT products from 1959-1979

Free Samples

7. These samples often do not appear on official medical records, and there is no way of tracing their use in patients. In 1969 Roussel stated that *'we ceased to promote*

Amenerone and Amenerone Forte in the United Kingdom several years ago.'.[6] Schering also reduced the number of samples given out,[7] see Table E.3 Samples of Primodos given out by Schering 1966 to June 1969, taken from Annex 3 of the EWG Report. There is no way to know how many of the samples that had been given out were used as pregnancy tests or how long they were kept for prior to use.

	1966	1967	1968	Up to June 1969
Samples given out	25,539	2,379	150	36

Table E.3 Samples of Primodos given out by Schering 1966 to June 1969

Proportion of HPTs used to test for pregnancy

8. Published estimation of the proportion of HPT prescriptions used for pregnancy testing varies considerably, see Table E.4 Estimates of the percentage of HPT prescriptions that were used for pregnancy testing. . This makes a substantial difference to the number of individuals exposed to HPTs *in utero*.

Percentage of prescriptions used as an HPT	Author
12.5%	Roussel Study 1968[8]
12%-20%	Dr Gal 1978[9]
75%-80%	Dr Gal 1972[10]
97%	Ministry of Health 1966[11]

Table E.4 Estimates of the percentage of HPT prescriptions that were used for pregnancy testing.

Prevalence of HPT use for pregnancy testing

[6] MH171_39 page 58
[7] Table 4 of Annex 3 'Updated Chronology' of the Report of the Commission on Human Medicines Expert Working Group on Hormone Pregnancy Tests 15 November 2017 available at https://www.gov.uk/government/publications/report-of-the-commission-on-human-medicines-expert-working-group-on-hormone-pregnancy-tests
[8] Roussel, *G.P Survey - An Investigation into the Effects of Oral Pregnancy Tests on the Incidence of C.N.S. Malformations.* Unpublished, 1968
[9] Gal I Teratological adverse drug effects: Review of evidence implicating hormonal pregnancy tests. available at https://mhra-gov.filecamp.com/s/GZdoZEG9hoT4o6nZ/fo
[10] Gal, I., *Hormonal Imbalance in Human Reproduction*, in *Advances in Teratology*. 1972
[11] MH 149_1105 page 16

9. In his 1974 paper Dr Inman writes *'The control data suggests that about 5% of fetuses are exposed to the test. This would be equivalent to about 40,000 exposures per annum.'*[12] In his report Dr Wiseman of Schering UK estimated that *'Only 10% of HPT-takers were pregnant. This figure is derived from the average between cases and controls in the British studies of Greenberg et al 1975 (a study which started in 1969), Laurence et al (1972) and Gal et al (1967).'*[13]

10. Schering UK records indicated that in April 1968, Dr. Briggs informed Dr. Gal *'that an independent market research institute on behalf of SCL had found out that 40% of all practising physicians in the UK were using the pregnancy test.'*[14] This does not say if they were exclusively using HPTs, or if HPTs were given to some women but not others, for example if an early diagnosis was required.

11. **Patient recall**. One possible way to trace use of HPTs is asking patients. There are a number of recognised practical difficulties with this approach; the number of years that have elapsed since HPTs were used may impact on individual recall; there is a recall bias where women who believe that the HPT detrimentally impacted on their pregnancy or their child will be more likely to remember taking it than women who do not attribute any significance to taking the HPT; the fact that medical records were less rigorous in the 1950s, 1960s and 1970s will inhibit cross checking; the findings that there were regional variation in HPT use would mean you would need to survey a variety of areas; and the many difficulties associated with tracing the numbers of women who were pregnant between 1953 and 1978.

Conclusion on how many women took HPTs

12. The combination of these factors makes it difficult to establish how many women were given HPTs as pregnancy tests. Given the limitations of all the available data it seems unlikely that it will ever be possible to know for certain the number of pregnancies where an HPT was used.

[12] CSM/AR BN116_19 Page 17.
[13] Wiseman R.A. *A Study of sales of HPTs and congenital malformations.* (undated, circa 1981) unpublished, available at Annex 13 of the EWG Report available at https://www.gov.uk/government/publications/report-of-the-commission-on-human-medicines-expert-working-group-on-hormone-pregnancy-tests
[14] LandesArchiv 13198 (trans) page 8 'Memorandum from Amon with a summary of Primodos' dated 23 September 1977

Pregnancy test options 1940-1980

13. It is important to remember that pregnancy testing has been revolutionised since HPTs were first on the market. A very brief synopsis will be given here to provide some historical context. Table E.5 Summary of the properties and availability of pregnancy tests in the UK 1940-1980 summarises the availability and properties of the main pregnancy tests available in the UK from 1930-1980. Figures on the cost of each test were taken from Dr. Jesse Olszynko-Gryn's presentation to the EWG.

Name	Type of test	Dates available in UK	Accuracy	Timeframe of test	Cost per test
Hogben test	Inject *Xenopus laevis* toads with women's urine then wait for a breeding response in the toad to indicate pregnancy. Could only be carried out in specialist labs.	Mid 1930s to mid 1960s	96-99%	Time to post sample (2-3 days), inject toad, wait 1 day, then post result (2-3 days) or phone (instant)	25/- (plus P&P)
HPTs	Hormonal preparation given (orally or by injection) then wait for a bleed to see if pregnant. Professional not involved in the test process itself.	1950 - 1978	96%	Usually two hormone doses 24 hours apart, then wait for a bleed, usually 2-3 days after.	5/-
Immuno- assays (e.g. Wampole's test, Pregnosticon, Prepuerin)	Blood or urine samples were mixed with human Chorionic Gonadotrophin (hCG) antibodies. If hCG was present the solution precipitated into clumps indicating and the woman was pregnant.	Mid 1960s onwards	By 1967 reported as 95-98%[15]	Time to post sample (2-3 days), test took 2 hours, then post result (2-3 days) or phone (instant)	£2 for private tests, cost to NHS unknown

[15] MH 156_663 page 15

	Could be done by local chemists or doctors				
Radioimmuno-assays	Urine or blood was mixed with a radioactive antibody to hCG. The level of radioactive binding followed the levels of hCG, so indicated if the woman was pregnant or not. Could only be carried out in specialist labs.	Mid 1970s - 1980s	As above	Time to post sample (2-3 days), test took 2-4 hours, then post result (2-3 days) or phone (instant)	unknown
Home test kits	Initially a variant on radioimmunoassays, improving as better technology became available. Done at home by woman, not by professionals.	1971 onwards	Initially high false positive, now highly accurate	2-4 hours	£1.75 initially

Table E.5 Summary of the properties and availability of pregnancy tests in the UK 1940-1980

Hogben or Toad Tests

14. During the 1950s and early 1960s pregnancy tests were provided by the NHS, but only to women with a pressing medical need for a diagnosis. The tests were slow, expensive and restricted. The Hogben (toad) test was carried out by some local hospital pathology labs and in three reference centres in Watford, Sheffield and Edinburgh.

Reimbursement for pharmacists

15. Medications supplied on prescription were dispensed by a pharmacist. The pharmacist bought stock from which they would dispense the treatment(s) that had been prescribed, the pharmacist would then claim a reimbursement from their regional Pricing Bureau for the dispensed stock. Most, though not all, HPT products were used for the following two different purposes:
    a. to diagnose pregnancy, and
    b. to treat secondary amenorrhea.

HPTs as Tests

16 Reimbursement for a diagnostic reagent used as part of a 'test' or 'diagnosis' was only paid if the reagent was on the List of Prescribed Reagents, see Table E.6 Reimbursement position for HPTs when prescribed during the mid-1960s. Primodos and Amenerone were not in the List of Prescribed Reagents.[16]

	Prescribed as a treatment	Prescribed as a test to diagnose pregnancy	
	In the Proprietary Index	In the List of Prescribed Reagents	Not in the List of Prescribed Reagents
HPT	Reimbursed	Reimbursed	Not reimbursed

Table E.6 Reimbursement position for HPTs when prescribed during the mid-1960s

HPTs as Treatments

17 Reimbursement of treatments was standard practice for products listed in the Proprietary Index, see Table E.6 Reimbursement position for HPTs when prescribed during the mid-1960s. For the first four months of 1966 both Primodos and Amenerone Forte were in the Proprietary Index,[17] so when they were used for the treatment of secondary amenorrhea reimbursement should have been routine. The three-tablet pack of Amenerone Forte was deleted from the Proprietary index in May 1966.[18]

The Subcommittee on Pregnancy Diagnostic Tests

18. During 1966 the provision of pregnancy testing by the NHS was discussed in by the subcommittee on Pregnancy Diagnostic Tests. This was a subcommittee of the DHSS' Central Pathology Committee.[19] There was considerable correspondence within various Ministry of Health departments on HPTs and also the use of UCG2 pregnancy tests (an immunological slide test).

The reimbursement of HPTs

[16] MH 149_1105 page 8
[17] MH 149_1105 page 33
[18] MH 149_1105 page 35
[19] MH 149_1105

19. In 1966 and early 1967 there was considerable discussion of the reimbursement for HPTs.[20] The two HPTs that held the majority of the market, Primodos and Amenerone Forte both came in two different pack sizes. Primodos came in a two-tablet pack and a 20-tablet pack. Amenerone Forte came in a three-tablet pack and a 20-tablet pack. The dosage used for treating short duration amenorrhea and pregnancy testing was the same, see Table E.7 Dosages of Primodos and Amenerone Forte as a pregnancy test and treatment of amenorrhea. Unless the prescription said something specific like 'for testing' or 'pregnancy test' it was difficult to know if the tablets were intended as a treatment or as a test.

	Primodos	Amenerone Forte
Pregnancy test	1 tablet daily for 2 days	1 tablet daily for 3 days
Secondary amenorrhea of short duration	1 tablet daily for 2 days	1 tablet daily for 3 days
Secondary amenorrhea of long duration	Not indicated for this	4 tablets daily for 5 days

Table E.7 Dosages of Primodos and Amenerone Forte as a pregnancy test and treatment of amenorrhea

20. Documents from 1966 indicate local variation with some areas refusing to reimburse prescriptions for the smaller packs of HPTs because they were 'tests' while other areas allowed them. This disallowing of reimbursement led to some letters of complaint from pharmacists and GPs.[21] This prompted calls for a unified approach and led to the gathering of information and expert views.

HPT prescription survey

21. As part of the discussions on HPTs a survey of prescriptions in May 1966 found 97% of the prescriptions were for the 2 or 3 tablet packages. The authors considered that these smaller pack sizes were for pregnancy testing, so concluded that almost all of the Primodos and Amenerone forte prescribed was for pregnancy testing.[22]

Expert views on HPTs

[20] MH 149_1105
[21] MH 149_1105 pages 40 and 60
[22] MH 149_1105 page 16

22. In October 1966 Dr J. G. Thomson, Senior Medical Officer at the Ministry of Health wrote several letters seeking expert views on the accuracy and desirability of using HPTs as tests.[23]

23. In a letter[24] dated 4 November 1966 Dr A. J. N Warrack, the Pathologist in charge of the Group Pathology Laboratory at the City General Hospital, Sheffield, replied stating *'I have consulted with one or two obstetric colleagues about these [HPTs] on previous occasions and the general opinion is that:-*

    (a) The test is unreliable

    (b) It may well be dangerous in that it could possibly precipitate abortion in a not well established pregnancy.

    The latter is very difficult to prove, of course, but this has certainly been suspected in one or two cases here.

    In general, therefore, I would not recommend the use of these materials for pregnancy diagnosis, although perhaps from the Laboratory point of view one is really not qualified to express an opinion.'

24. A reply from Dr Bruce Hobson of the Department of Obstetrics and Gynaecology, University of Edinburgh dated 4 November 1966[25] describes HPTs as *'not too inaccurate'* and goes on to state: *'My objection is that there are more accurate tests which do not require steroids to be taken by the women. These "withdrawal bleeding" tests should not be done by women who may have difficulty in retaining an early conceptus. It is well known these tests will restore menstruation soon after a missed period. Many of these cases are undoubtedly early abortions. In the series Dr. Matthew and I investigated we had 12 abortions in 83 pregnant women after using Disecron.'*

Safety concerns

25. It is clear that the Ministry of Health (MoH) had been informed that there were safety concerns relating to abortions following HPT use. These concerns were anecdotal and not conclusively proven, but in response to MoH enquiries at least two independent experts would not recommend HPTs.

[23] MH 149_1105 page 55
[24] MH 149_1105 page 55
[25] MH 149_1105 page 56

Pregnancy Test Service reorganization

26. In 1966 the Subcommittee on Pregnancy Diagnostic Tests recommended reorganizing pregnancy testing services. The subcommittee recommended phasing out the Hogben tests and replacing them with immunoassays. They concluded that Pregnosticon and Prepuerin were reliable and accurate.[26] Accordingly, these immunoassays were placed on the Central Supply list from 1 February 1967,[27] and arrangements were put in place for these tests to be carried out in hospital pathology labs at the request of GPs.[28]

Immunological test service

27. A letter dated 7 August 1967[29] was sent from the Ministry of Health to Regional Hospital Boards and Boards of Governors of teaching hospitals. This letter describes how testing at the Hogben "Toad" test centres had been limited to certain situations *'In practice such requests from general practitioners were usually accepted only on medical or socio-medical grounds.'* The letter goes on *'The Department now recommends that the hospital authorities should arrange for pathology laboratories to accept requests for pregnancy tests on referral form general practitioners and should discuss the introduction of the new arrangements with Local Medical Committees. The requests could be met effectively by using immunological reagents.'* It continued *'Senior Administrative Medical Officers were informed at their meeting on 20 September 1966 that, in order to help hospital authorities to provide this wider service, the Department was placing Pregnosticon and Perpuerin on central supply. These reagents are now available… This arrangement is not intended to preclude the use of other reagents by pathologists.'* A copy of this letter was also sent to County and County Borough Councils; London Borough Councils; Common Council of the City of London; and Greater London Council. Once implemented all GPs should have been able to utilise laboratory-based immunological pregnancy testing in local hospitals for all women.

[26] MH 149_1105 page 3
[27] The documents in the file record two start dates, 1 January and 1 February. Other contemporaneous documents indicate that the services were not in place on 1 January.
[28] MH 149_1105 page 3
[29] MH159/78 Letter from Mrs E Croft, Ministry of Health Reference G/H118/01 dated 7 August 1967 to Secretaries, Regional Health Boards.

28. From 1967 onwards there was a centralized laboratory service that GPs could use to test for pregnancy. Just because it was available does not mean it was used. In 1960 two Bristol GPs had outlined reasons why laboratory-based urine pregnancy testing was inconvenient.[30] *'Although the results of the test may be known in twenty-four to forty-eight hours, there may be several days' delay beyond this before the result reaches the practitioner. In addition, the collection and transmission of the specimen represent a considerable inconvenience to an already busy person.'*

Continuing Hormone Pregnancy Test use

29. When the laboratory pregnancy testing service was provided there does not seem to have been any attempt to discourage GPs from using HPTs. HPTs were left on the Proprietary Index and were reimbursed as standard, regardless of the pack size prescribed. The indication for pregnancy testing remained for HPTs until 1970, so there was nothing to prevent a doctor from prescribing an HPT product as a pregnancy test.

HPTs as abortifacients

Abortifacient – a substance that causes an implanted pregnancy to abort (miscarry)

Emergency contraceptive – a substance that stops a pregnancy from occurring by preventing a fertilised egg from implanting into the womb lining.

30. We have heard that HPTs were believed to act as abortifacients. When HPTs were introduced to the UK market in the 1950s abortion was highly restricted. Free of charge legalized abortion on the NHS became available from 27 April 1968 under the Abortion Act 1967. Access to reliable contraception was also far more limited in the 1950s and 1960s; although the combined oral contraceptive pill was introduced in 1961 it was only prescribed to married women until 1967.

Menstranol

[30] Higgins, G.L. and W.R. Sadler, *A two-tablet oral pregnancy test.* Practitioner, 1960. **185**: p. 677-80.

31. The LandesArchive files[31] (13226) indicate that Schering had tested a compound, ZK 4.944[32] (Menstranol) as an emergency contraceptive in rats. Menstranol converts to ethinylestradiol (one of the components of Primodos) in the body. Menstranol was used (in combination with a progesterone) in early combined oral contraceptive pills available in the UK.[33] We have seen no evidence that Menstranol was ever licensed and indicated as an abortifacient the UK.

Primodos indications

32. We have received written evidence from Bayer,[34] who purchased Schering in 2006, that Primodos was never indicated or licensed for this use and the Schering never sought to add this as an indication nor obtained a licence for this use.[35]

UK perceptions about Primodos

33. There was clearly a view held by some UK doctors and experts that HPTs could induce an abortion. The National Archives contain reports from 1966 made by two UK experts expressing views that HPTs may disrupt an early pregnancy, see paragraphs 2322 and 24. Dr Dean's preliminary results described in an extract of 'The Outcome of Pregnancy Study' (unpublished, dated 1968)[36] records four abnormalities from 135 women given HPTs (79 were Primodos). A high rate of abortions was noted in the Primodos group. Dr Dean states *'the figure of 10% abortions recorded after Primodos is unlikely to be due to chance.'* [37]

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[31] LandesArchive files 13226 (translation) page 112. *'ZK 4.944 (ethinyl oestradiol) Testing for embryotoxic effects in rats.'* The 17 April 1973 report on study ZK 4.944 on rats found a dose-dependent embryo-lethal effect at doses of 0.1 mg/kg and 0.3 mg/kg and could not rule out a teratogenic effect. At doses of 0.03 mg/kg no embryolethal or teratogenic effects were detected. The question of embryo-lethal and teratogenic effects of ZK 4.944 were not addressed any further as it was stated that ZK 4.944 was intended to be used for the emergency post-coital prevention of pregnancy

[32] 17α-ethynyl-oestra-1,3,5(10)-triene-3,17-diol

[33] In the current BNF entry on norethisterone with menstranol the section entitled 'Pregnancy' reads 'For all COMBINED HORMONAL CONTRACEPTIVES Not known to be harmful'. https://bnf.nice.org.uk/drug/norethisterone-with-mestranol.html

[34] Bayer Written evidence

[35] See; OH ACDHPT 20 May 2019 and Bayer Right of Reply dated 18 July 2019; OH APPG on HPTs 14 May 2019 and Bayer Right of Reply dated 19 July 2019; and Bayer written Evidence response to Q3

[36] CSD/AR *MH 171_39.* Page 48

[37] In a broadly contemporaneous survey of almost 4,000 pregnancies Warburton & Fraser 1964 record that 14.7% of all pregnancies aborted before 6½ months gestation, see Warburton, D. and F.C. Fraser, *SPONTANEOUS ABORTION RISKS IN MAN: DATA FROM REPRODUCTIVE HISTORIES COLLECTED IN A MEDICAL GENETICS UNIT.* Am J Hum Genet, 1964. **16**: p. 1-25.

34. There are published reports that HPTs were used to attempt an abortion in the UK.[38] In his letter to Dr Inman dated 14 June 1967 Professor Smithells wrote *'Certainly in this part of the world pregnancy test drugs are prescribed on a fantastic scale and are quite often prescribed during the second trimester of pregnancy. I think there is a widespread belief amongst the laity that these drugs are abortifacient and I suspect that they are sometimes obtained from G.P.s by giving a misleading history.'*

35. This issue was explicitly detailed by Isabel Gal in her 1972 paper.[39] *'Probably because of their menorrhagic property, the tablets are frequently used to induce abortion. Similar trends were noticed amongst our study cases, who were taking the pregnancy test tablets. In all but one of the 19 index cases, the pregnancy was unwanted (these included 2 illegitimacies) and, of the 4 control cases, one was a contraceptive failure, and 3 were illegitimate pregnancies. Thorough investigations did not reveal any other attempts to terminate the pregnancy in the above cases.'*

36. Dr Gal's 1972 paper indicates that overdosing of HPTs occurred in the UK *'All the 23 mothers who took pregnancy test tablets received them without any prescription (supplied from medical samples – all confirmed) and two of them obtained a second dose from the chemist.'* Brotherton & Craft 1972[40] also recorded *'7 patients had had an oral hormonal "pregnancy test." Two of the latter patients had taken much more than the recommended dose of 2 or 3 tablets. In all cases where an oral pregnancy test had been taken, the actual abortion occurred some weeks later.'*

International perceptions about Primodos

37. In the late 1970s Schering Germany were aware of contemporaneous references to the belief that Primodos may act as an abortifacient.[41] *'Our Korean interlocutors told us that in this case, hormonal pregnancy diagnosis is practically irrelevant. Women who desire to have children primarily go to the doctor, who uses an extracorporeal test. These women do everything to keep their child from harm. Women who do not*

[38] For example, see Gal, I., *Risks and benefits of the use of hormonal pregnancy test tablets.* Nature, 1972. **240**(5378): p. 241-2; Gal I Teratological adverse drug effects: Review of evidence implicating hormonal pregnancy tests. available at https://mhra-gov.filecamp.com/s/GZdoZEG9hoT4o6nZ/fo
[39] Gal, I., *Hormonal Imbalance in Human Reproduction*, in *Advances in Teratology*. 1972.
[40] Brotherton, J. and I.L. Craft, *A clinical and pathologic survey of 91 cases of spontaneous abortion.* Fertil Steril, 1972. **23**(4): p. 289-94
[41] LandesArchiv (translation) 13193 *'Attachment to SL-minutes 246 / TOP'* dated 19 June 1978' page 62

wish to keep their pregnancy (mainly those engaged in entertainment) will, however, first go to a pharmacist with the desire to obtain a remedy that triggers a haemorrhage. As a rule, overdosing is used in an abortive manner. If the bleeding does not occur and the woman is pregnant, she has an abortion (semi-legal). It is not out of the question, however, that pregnant users do not want an abortion, although the Korean management does not believe in such cases. We could not obtain any information about the size of this group, nor were we able to obtain any indications of the incidence of abortion.' This view that Primodos could act as an abortifacient appears to have been held by doctors in Germany as well *'In conversations about Duogynon it was highlighted that a surprisingly high percentage of physicians still swear by accomplishing an abort through Duogynon.'*[42]. There are also reports that HPTs were used in this way in Israel.[43]

38. We have heard from Dr Olszynko-Gryn[44] that HPT use in the belief that these were an *'off-label abortion pill'* was more common in countries where access to abortion was more restricted, such as Germany. This has been echoed in some of the more recent papers from less developed nations with restricted access to legal abortions, for example the Bonnema & Dalebout paper[45] describing Peru in 1987.

39. We have heard in oral evidence that products that have the same ingredients and formulations as HPTs are still available in the developing world, and that there is a belief that this is because they are thought to act as abortifacients.[46] We have seen evidence of HPTs used as pregnancy test in less developed countries long after use in developed nations had stopped, for example in 2007 Neogi[47] reports the use of progesterone analogues to test for pregnancy in India despite an official contraindication on use in pregnancy having been in place for over 30 years.

[42] LandesArchiv 13223 (translation) '*Memo from Dr Smolarek'* (Schering AG, Hannover) dated 18 August 1978 Pg 82
[43] Harlap, S., R. Prywes, and A.M. Davies, *Letter: Birth defects and oestrogens and progesterones in pregnancy.* Lancet, 1975. **1**(7908): p. 682-3
[44] OH Dr Olszynko-Gryn 26 November 2018
[45] Bonnema, J. and J.A. Dalebout, *The abuse of high dose estrogen/progestin combination drugs in delay of menstruation: the assumptions and practices of doctors, midwives and pharmacists in a Peruvian city.* Soc Sci Med, 1992. **34**(3): p. 281-9
[46] OH ACDHPT 20 May 2019
[47] Neogi, S.B., *Congenital malformations: unexplored causes.* Indian Pediatr, 2007. **44**(12): p. 941.

40. The historical context is important, a 1952 published paper by Winkelstein[48] presents a very different slant on the potential link between use of withdrawal -bleed pregnancy tests and abortion. *'…a test for pregnancy, possesses a definite psychologic advantage, from the patient's viewpoint, that the doctor "is doing something positive" both in the way of diagnosis and of therapy if the delay is physiologic. Although the physician realizes that it is not essential to bleed at clocklike intervals, it is often difficult to convince a worried female who knows only that suspended menses is indicative of pregnancy. There is no question, therefore, that the use of this drug, with its diagnosis dependent upon the resumption of menstrual function, will keep a great many women from unnecessary manipulations at the hand of the abortionist. Furthermore, the resumption of the normal menstrual rhythm in the nonpregnant is a great psychologic factor, especially when pregnancy is not desired at the time that the menses is delayed.'*

41. The 2017 Expert Working Group on Hormone Pregnancy Tests Report considered the anecdotal evidence, the mechanistic evidence (both animal and clinical studies) and the epidemiological evidence on the use of HPTs as an abortifacient. They concluded that there was no evidence that administration of HPTs at the licensed dose during early pregnancy was associated with an increased risk of miscarriage.

42. The accuracy of the claims that HPTs acted as an abortifacient fall outside the Review's scope. However, we have considered how the regulators and manufacturers used any knowledge they had of the use of HPTs and any subsequent miscarriages or abortions to inform our thinking.

[48] Winkelsteint, L.B., *Prostigmine methylsulfat and delayed menstruation: Evaluation of prostigmine as a test for pregnancy.* American Journal of Obstetrics and Gynecology, 1952. **44**(2): p. 231-239