HORMONAL PREGNANCY TESTS

Committee Alerts Doctors

The Committee on Safety of Medicines have sent to all doctors in the United Kingdom a letter informing them of a possible association between hormonal pregnancy tests and an increased incidence of congenital abnormalities. They recommend that, in view of the possible hazard, doctors should not normally prescribe certain hormonal preparations for pregnancy tests. The full text of the Committee's letter is attached.

Their preliminary findings have emerged from a wider study which is being undertaken to detect any relationship between congenital abnormalities and the use of drugs during pregnancy. This large scale investigation is still in progress but where necessary, as in this case, preliminary results are reported if a possible hazard is suggested.

The Committee have already published an early warning letter in the British Medical Journal. As further evidence accumulated they felt it right that all doctors should be made aware, at this stage, of the Committee's provisional conclusions, particularly as other means of diagnosing pregnancy are available. They emphasise that these are preliminary conclusions. The outcome of the study will be made known when it is completed later this year.

Similar action is currently being taken by drug regulatory authorities in several other countries.

4 June 1975

Issued by the Department of Health and Social Security (01-407 5522) on behalf of the Committee on Safety of Medicines.
HORMONAL PREGNANCY TESTS:
A possible association with congenital abnormalities

A number of studies have shown a possible association between taking mixtures of an oestrogen and a progestogen as a means of diagnosing pregnancy and an increased incidence of congenital abnormalities.

The Committee on Safety of Medicines wish to draw attention to these studies and to the preliminary results of their own case-control study. The early results suggest that a relatively greater proportion of mothers of abnormal babies had been tested in this way. A letter describing these preliminary results was published in the British Medical Journal on April 26, 1975. (Greenberg, et al, ii, 191). The Committee will present their further conclusions later in the year, when their study is completed.

On the present evidence, the Committee believe that it is possible that the use of these preparations for the diagnosis of pregnancy could on occasion lead to abnormalities in the foetus. There are other means of diagnosing pregnancy which do not require the administration of hormones, and the Committee consider that in view of this possible hazard this method should not now normally be used.

As the data began to accumulate it was felt advisable to inform the companies known to be concerned and it was ascertained either that they had ceased to promote the products for this use, or that the product had been removed from the market. With this further evidence of this possible hazard, the Committee have advised the Health Departments that measures should be taken to ensure that this indication is not included in licences for such products and to require the insertion in all promotional literature of a warning about this possible hazard in pregnancy.

As far as is known the hormone preparations which have been, at some time, used or recommended for this purpose are:

- Amenorone
- Amenorone Forte
- Discron
- Menstrogen
- Norlestrin
- Norlutin A
- Norone
- Orasecron
- Paralut
- Pregornot
- Primodos
- Secrody1

Some of these products are no longer on the market, whilst others will continue to be marketed for the treatment of a variety of conditions in women who are not pregnant.
13.1 Hormonal Pregnancy Tests

The Sub-Committee were aware that a number of other drug regulatory authorities had issued papers drawing attention to hazards which may be associated with hormonal pregnancy tests, that an article had been published in "Nature" in 1967 on the same subject and that a representative of the Sunday Times was enquiring what action the Committee on Safety of Medicines were taking in the matter. There was a suggestion that the Committee may have a legal obligation to advise the medical profession of hazards as soon as they knew about them. The preliminary results of the Committee's case-control study had been published in the BMJ of 26 April. Although they would have preferred to wait for the completion of the study, they felt that it was necessary, in view of the action by other drug regulatory authorities and of the public's concern, to issue a statement without delay. They recommended therefore that a leaflet in the Adverse Reactions Series be issued, and has prepared a draft for this purpose. The Committee agreed to this course of action (see Item 14 below).

13.2 Oral Contraceptives and Chromosomal Abnormalities

The Sub-Committee's view of the paper to be considered by the Committee (see item 8 above) was that it did not present evidence to demonstrate that there was an absolute increase in the risk to subsequent pregnancies and that there were alternative hypotheses.

13.3 Dissemination of Information

From time to time the Sub-Committee had considered ways of disseminating information about adverse reactions. They had now reached an opinion that a yellow leaflet in the Adverse Reactions Series was not always appropriate and that a regular publication might be issued on less urgent topics. At an earlier meeting they considered that a suitable title for such a new series might be "Current Problems in Adverse Drug Reactions." They recommended that such a publication should be prepared as an experiment and published before the Conference on the dissemination of information which is to take place in October. This would give the Committee an opportunity of gauging the profession's response to such a document without committing the Committee to publishing such a document as a regular feature. The Committee approved this proposal.

13.4 Indomethacin

The Sub-Committee had considered a letter from Professor Watson Buchanan commenting on his experience with adverse reactions in relation to indomethacin. In his view cerebral symptoms were dose related, but
considered that it might be valuable to contact Professor Watson Buchanan again and invited Professor Vere to act as a convener of a multi centre study with Dr Davies and Professor Watson Buchanan. The Group were asked to study the relationship of adverse reactions to indomethacin to dose levels and to examine the extent of hypertension reported. Although it had been suggested that it might be necessary to contact doctors who had reported such adverse reactions in order to follow up their patients, the Committee did not approve this proposal at this stage. They thought that initially the group should follow up the patients under their own care.

13.5 Beta-Blockers

The Secretariat had reported on the information available on psoriasisform rashes and eye involvement occurring in patients receiving oxprenolol, propranolol and tisolol. The Sub-Committee did not consider the sending of a leaflet in the Adverse Reactions Series was justified, however, at this stage. They thought that it would be more appropriate for a letter to be sent from the Secretariat to the professional press drawing attention to the report and recommended accordingly.

The Committee agreed that a preliminary warning should be given. They thought that this might be done by including an item in the proposed publication "Current problems in Adverse Drug Reactions" (paragraph 13.3), and asked the Secretariat to prepare a draft on this basis.


Since the meeting of the Sub-Committee on Adverse Reactions an article had been published in the Sunday Times, which drew attention to the possibility of congenital deformities appearing in the children of mothers who had had pregnancy diagnosed by this method. This had stimulated a considerable amount of press interest and in the light of this a further revision of the draft warning notice had been prepared in consultation with the Chairman. A copy of this was put before the Committee for its approval, and issue of a letter along these lines was agreed. The Committee also advised the Health Departments that measures should be taken to ensure that this indication is no longer included in licences for such products and to require the insertion in all promotional literature of a warning about this possible hazard in pregnancy.
HORMONAL PREGNANCY TESTS:
A possible association with congenital abnormalities

COMMITTEE ON SAFETY OF MEDICINES

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On the present evidence, the Committee believe that it is possible that the use of these preparations for the diagnosis of pregnancy could on occasion lead to abnormalities in the foetus. There are other means of diagnosing pregnancy which do not require the administration of hormones, and the Committee consider that in view of this possible hazard this method should not now normally be used.

As the data began to accumulate it was felt advisable to inform the companies known to be concerned and it was ascertained either that they had ceased to promote the products for this use, or that the product had been removed from the market. With this further evidence of this possible hazard, the Committee have advised the Health Departments that measures should be taken to ensure that this indication is not included in licences for such products and to require the insertion in all promotional literature of a warning about this possible hazard in pregnancy.

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- Pregnorot
- Primodos
- Secodyl

Some of these products are no longer on the market, whilst others will continue to be marketed for the treatment of a variety of conditions in women who are not pregnant.
COMMITTEE ON SAFETY OF MEDICINES

Your reference:
Our reference: CSW/AR/159

Finsbury Square House
33/37a Finsbury Square
LONDON, EC2A 1PP
Telephone: 01-638 6020

16 November 1977

Dear Sirs,

ADVERSE REACTION LEAFLET – HORMONAL PREGNANCY TESTS

Enclosed for your information is a copy of Leaflet No. 16 in the Adverse Reaction Series which is being sent to all doctors, hospital principal pharmacists and retail pharmacists in the UK on 17 November.

I should be grateful if you would ensure that no publicity is given to the contents of the leaflet before the morning of 18 November at the earliest.

Yours faithfully,

[Signature]

P. HARDWICK

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HORMONAL PREGNANCY TESTS AND CONGENITAL ABNORMALITIES: A further statement

COMMITTEE ON SAFETY OF MEDICINES

In June 1975 the Committee on Safety of Medicines published a warning about a possible association between Hormonal Pregnancy Tests and congenital abnormalities (Adverse Reactions Series No. 13).

That publication was based on preliminary evidence: further results have now been published (Greenberg, et al, British Medical Journal 1977, 2, 853-856) and the association is confirmed.

The Committee therefore reiterate their view, expressed in their earlier warning (which is attached) that hormonal tests for pregnancy should not be used.

Alternative methods are available which are free from this risk.

Most of the preparations referred to in the earlier leaflet were removed from the market. The data sheets for those which remain for other indications state clearly that pregnancy is a contraindication to their use.
was now considering an advertising campaign to encourage parents to have their children vaccinated against tetanus and diphtheria as well as pertussis and was seeking the Committee's views on the subject.

20.2 There was some discussion as to whether the campaign had in fact started, because some members had recently seen or received literature on the subject. It was agreed that the Secretary of State should be advised that the Committee were unable to comment on the crude figures before them, but, in the light of the current concern and their knowledge that an examination of a number of cases is at present being undertaken, they doubted whether this is an opportune time to promote an advertising campaign for pertussis vaccine.

20.3 Hormonal Pregnancy Test (Tabled Paper)

The Chairman said that a recent article in the General Practitioner had suggested that Primodos was still being prescribed for pregnancy tests. In addition there had been further suggestion to this effect in the media, including a recent television programme. He also drew attention to the letter which Schering Chemicals Ltd had sent to doctors on 14 October, and to a further letter from the Company which suggested 9.3% of total prescriptions for Primodos from July 1976 to June 1977 had been for use in pregnancy testing. In these circumstances he considered that it would be advisable for the Committee to send a further warning leaflet to doctors, reminding them of the possible hazards and drawing attention to the recently published article by Greenberg et al.

20.4 It was accepted that, while the quantitative assumptions about usage made in the General Practitioner article were questionable, any prescribing of Primodos or similar products for pregnancy testing was unacceptable. Some members stated that such prescribing had been drawn to their attention recently.

20.5 The question of whether the Committee's warning leaflets should be used for such reminders or whether they should be reserved for new dangers was raised. After it had been pointed out that the alternative was to advise the licensing authority to take action under Section 62 of the Medicines Act, it was accepted that there was no objection in principle to the use of the leaflets in the manner suggested where an issue of such potential danger was involved.

20.6 The Committee agreed that a new warning leaflet should be sent as soon as possible, the wording of which was to be decided by the Secretariat, in consultation with the Chairman.

21. Date and time of next meeting

24 November 1977 at 11 a.m.

22. For Information

Phenformin and Biguanides/B Adrenoceptor Blockers

- Warnings by National Drugs Advisory Board - Paper 1.