LESSONS FROM HISTORY

Diethylstilbestrol — haunting lessons

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In the late 1940s a breakthrough study on the progress and outcome of pregnancy using the synthetic oestrogen diethylstilbestrol (DES) as an intervention was published by Smith *et al.* from Boston, USA.[1] The hypothesis originated from sound physiological experimentation showing that pregnant oophorectomised rats ended up with miscarriages.[2] Laboratory evidence in the 1940s was proposed to support the concept that reduced placental hormone production was associated with a variety of adverse pregnancy outcomes. A clinical trial was embarked upon in the Boston Lying-in Hospital between 1947 and 1949 to substantiate the effect of DES. The trial was not randomised or placebo-controlled. The summary of the findings indicated a reduction in the incidence of pre-eclampsia, prematurity, low birth weight, stillbirth, and postmaturity.[1]

The DES intervention became popular in the early 1950s and beyond.

In 1953, Dieckmann *et al.*[3] conducted a randomised double-blind placebo-controlled study using a similar dosing regimen to that of Smith from about 16 weeks of pregnancy. They did not find any difference in prematurity rate or decrease in the incidence of perinatal mortality. There was also no decrease in pre-eclampsia in the DES-treated group. The Dieckmann trial was presented at the 1953 annual meeting of the American Gynecological Society. During the discussion time, Smith remarked: 'our experience with the use of stilbestrol continues to be satisfactory . . . We are convinced that it has reduced the complications of late pregnancy and saved many babies. We trust that many obstetricians who have been following our recommendations for the use of stilbestrol in pregnancy will realize that the report this morning [Dieckmann's] fails to provide definite evidence as to the contrary.' Several reports from the USAand Britain soon followed that supported the Dieckmann findings.[4,5]

Despite the overwhelming evidence of the later trials against DES, use continued unabated. More than 3 million women were exposed to it between the 1950s and early 1970s. Women were excited at this 'wonder' drug and doctors were happy as there were no known side-effects and the study by Smith was 'convincing'.

In the 1970s some cases of an extremely rare vaginal cancer, adenocarcinoma, occurred in young women in the Boston area of the USA. Taking into cognisance the rarity of this carcinoma, an epidemiological search was launched which revealed that these young women had been exposed to DES *in utero.*

Thereafter, an intensive investigation of the offspring of DES-treated women was mounted. Compared with those whose mothers had received placebo treatment in the original randomised trials, those exposed to DES *in utero* had a significant increase in health problems. A meta-analysis[6] summarises the follow-up of the exposed women and their offspring. Antenatal DES exposure has not been shown to be of benefit in preventing adverse fetal outcome. The miscarriage rate, preterm labour, birth weight, stillbirth or neonatal deaths were not positively influenced by the intervention compared with the control group. Maternal outcome in terms of pre-eclampsia and survival of mothers was not influenced. Exposed daughters had a non-significant trend towards more cancer of the genital tract and other cancers. Primary infertility in daughters, adenosis of the vagina/cervix and testicular abnormality in sons were significantly higher in those exposed to DES before birth.

Lessons learned

It is 50 years since Dieckmann's publication — DES is no longer in use, but the lessons learned should not be forgotten. More than ever we need properly designed clinical trials, coherent and standardised systematic reviews, evidence-based clinical practice and strategies to disseminate research information. The original trial by Smith was designed to test what appeared to be a biologically attractive hypothesis. Randomisation was by alternate allocations 'so far as was possible', in primigravid women attending antenatal care. Placebo was not used. Three hundred and eighty-seven women were allocated to the DES group and 555 to the control group.

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The methodological quality of the study allowed for the possibility of bias in group allocations. Alternative allocations should yield fairly equal numbers in each group. It is possible that assumptions about the effectiveness of the intervention influenced treatment group allocation.

We must ensure that personal assumptions don't unduly influence our management decisions. When most patients treated in a certain way feel better, health workers tend to assume that the treatment must be effective, forgetting to consider the power of the placebo effect. It is only through use of double-blind, placebo-controlled trials that one realises that people treated with placebo also get better. For a treatment to be confirmed effective, it must be shown to work better than placebo. Objective evidence of effectiveness is needed because all interventions may have potential unexpected or idiosyncratic adverse effects.

It may not be feasible to keep up with the medical literature as several million articles are published annually, but this problem is not insurmountable with the introduction of systematic reviews. Such reviews, published for example in the Cochrane Library, have a well-defined structure and objectives. They take considerable time and effort to prepare and update. Cochrane Systematic Reviews have additional advantages: they follow a standardised format; the methods used to prepare them follow strict protocols; and where appropriate, they present the results of each trial included in the review graphically, with the possibility of conducting meta-analysis with summary estimates such as relative risk or odds ratio, and heterogeneity tests. The characteristics of each study included in the review and the overall results are presented in tables in a structured, standard format. These features render the reviews transparent in terms of the data, inclusion and exclusion criteria, and nature of the analysis applied to the data.[7]

Another resource relevant to the developing world is the Reproductive Health Library published by the World Health Organisation (WHO),[7] which includes reviews from the Cochrane Library of relevance to reproductive health care in resource-poor countries. The electronic data on compact disk are distributed freely to organisations and individuals. The information has been transparently and rigorously reviewed by experts on the subject. These systematic, up-to-date summaries constitute reliable evidence of the benefits and risks of health care and are intended to help policy-makers and clinicians make sound practical decisions. It is detrimental not only to the medical objective of effective care, but also to the allocation of meagre developing world resources, to allow practices of unknown effectiveness, or practices that are known to be harmful, to become entrenched in medical practice. The gradual introduction of systematic reviews over the past two to three decades means that disastrous interventions and personal opinions, as with DES, will have less chance of gaining general acceptance.

Modern health practices emphasise the importance of consumer satisfaction. The women during the DES era were enthusiastic about the drug; however, consumers are influenced by the information provided. The information available 50 years ago on the ineffectiveness of DES was not readily accessible to consumers. The issue of lack of access to information is currently being addressed globally, with access to the Internet, electronic reviews and other traditional means of disseminating health information.

The ideal of evidence-based care will be closer to being realised and the regrettable DES saga may never again be repeated if the story of DES serves as a positive and not-to-be-forgotten lesson.

However, the onus is on individual physicians to change practices on the best available evidence so that the overall objective of health care, namely 'to do more good than harm', may be achieved.

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