Mira Harrison-Woolrych
Editor

Medicines For Women

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Prescribing Medicines for Women: General Principles and Consideration of Special Sub-populations

Chapter 1
Medicines for Women: Medicines for Half the World

Mira Harrison-Woolrych

Introduction

Medicines for women are not a minority issue: women represent half our worldwide population and at all ages women take more medicines than men (Kaufman et al. 2002). A population survey conducted in the United States (USA) showed that 89 % of women aged 45–64 years took at least one medication – including prescription and non-prescription medicines – and 43 % in this age group took five or more medicines (Kaufman et al. 2002). Women primarily take responsibility for contraception (Ringheim 1993) and mothers are responsible for administering medicines to babies – both before and after delivery – and to children too. The health of women determines the health of families and of wider communities, so we all have a vested interest in the medicines women take throughout their lifetimes.

In this book many issues concerning medicines for women are brought together for the first time in one volume. There have of course been other texts on specific groups of medicines for women (for example, contraception, medicines in pregnancy) and thousands of research publications on individual medicines, but my aim in editing this book was to construct a work which pulled the focus onto the subject of women's medicines: to recognise women as important – and often vulnerable – consumers of medicines and address some of the issues which prescribers, healthcare workers, patients and their families face on a daily basis around the world.

In this opening chapter, I begin with some historical and social perspectives which provide the backdrop for the setting in which medicines for women are prescribed. I then present an overview of the following 18 chapters of this book, in which I summarise and comment on some of the most significant issues associated

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with the medicines, vaccines and devices available for women today. Amongst the technical evidence-based information presented in each chapter, there are many fascinating stories – some familiar and some less so – and important themes emerge throughout this book.

In the latter part of this chapter we discuss some general principles about prescribing medicines to women, again drawing on the valuable information provided in each of the other chapters. Finally, I present some conclusions from this book and how we might move forward from here.

Historical and Social Perspectives

Women have been using medicinal products for at least 2,000 years. Soranus was a Greek physician who practised medicine in Alexandria, Egypt and later in Rome during the first part of the second century A.D. He wrote a four-volume work on gynaecology which included the following advice on contraception (Shelton 1998):

> It is safer to prevent conception from occurring than to destroy the fetus through abortion. . ..therefore one must avoid intercourse at those times which we said were favourable for conception. . .It also helps, in preventing conception, to smear the entrance to the uterus with old olive oil or honey or sap from a cedar or balsam tree, alone or mixed with white lead. . ..One might also add a clump of finespun wool. . .

The first part of this statement is very enlightened for its time, but it is sensible (perhaps even obvious) advice which remains true today. The latter part of Soranus' text above, reveals some of the contraceptive products which women were advised to use in the second century AD. It is difficult to know whether women actually used these methods and if they did, how effective and safe they were. But this text shows that medicines for women have been a feature of gynaecological practice for the duration of the speciality itself.

It is also likely that women before this time were using their own treatments for female disorders and for prevention of pregnancy. A tutor at a family planning course in the UK told us that women have known for centuries that half a lemon could be inserted into the vagina for use as a cervical cap. She would not be drawn on the details of how effective or safe (or comfortable) this was, but advised that one advantage of the lemon method was that the other half could be used in a gin and tonic, either before or after coitus!

The history of medicines and devices for women to use as birth control is closely linked to the history of women's development in many socio-cultural and economic respects. It has been a key component in movements for gender equality and women's rights, as the ability to limit family size is an important factor in determining not only women's and children's health, but also in determining women's opportunities (van der Gaag 2008). The broader aspects of women's lives are the backdrop against which medicines for women are prescribed, researched and

monitored. Throughout this book we will learn that the environment in which women live is a key factor determining how medicines are used and how effective and safe they are in real life use.

Marketing Medicines for Women: Early Tragedies for Women and Their Babies

The history of medicines for women has been central to the history of pharmacovigilance – the specialty which monitors the safety of medicines worldwide. This theme is developed further in Chap. 15 on medicines regulation and is well illustrated in Fig. 15.2 of that chapter (p. 437). Pharmacovigilance in many countries began in the wake of the tragic story of thalidomide, when women and their babies became the innocent victims of a medicine designed to relieve morning sickness of pregnancy. Dr WG McBride, an obstetrician and gynaecologist from New South Wales, Australia was the first to report the shocking limb deformities he noticed in babies born to women who had taken thalidomide (Distival®). His short but effective letter to the Lancet in 1961 is shown in Box 1.1:

Box 1.1: Text of Dr WG McBride's Letter to the Lancet, 1961
Thalidomide and Congenital Abnormalities

"Sir – congenital abnormalities are present in approximately 1.5 % of babies. In recent months I have observed that the incidence of multiple severe abnormalities in babies delivered of women who were given the drug thalidomide ("Distival") during pregnancy, as an antiemetic or as a sedative, to be almost 20 %.

These abnormalities are present in the structures developed from mesenchyme – i.e. the bones and musculature of the gut. Bony development seems to be affected in a very striking manner, resulting in polydactyly, syndactyly, and failure of development of long bones (abnormally short femora and radii).

Have any of your readers seen similar abnormalities in babies delivered of women who have taken this drug during pregnancy?"

WG Mc Bride, Hurstville, New South Wales

Lancet Editor's note – *in our issue of December 2 we included a statement from the Distillers Company (Biochemicals) Ltd. referring to "reports from two overseas sources possibly associating thalidomide (Distival) with harmful effects on the fetus in early pregnancy". Pending further investigation, the company decided to withdraw from the market all preparations containing thalidomide.*

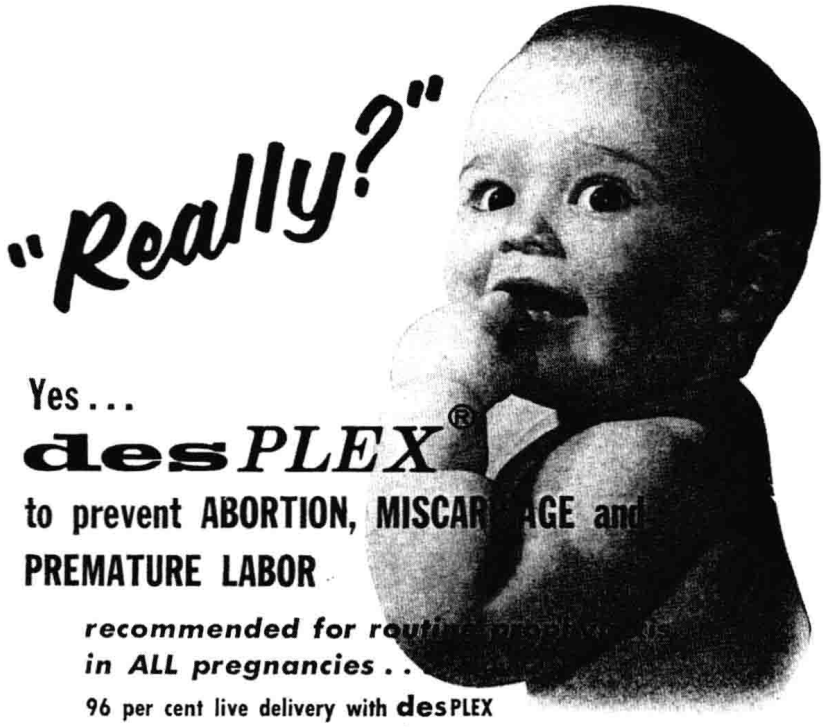

Fig. 1.1 1950s advertisement for desPlex (diethylstilboestrol)

In addition to thalidomide, there have been other lesser-known tragedies relating to medicines for women. From the late 1940s onwards, diethylstilboestrol (DES) was widely prescribed to pregnant women for prevention of miscarriage and desPlex® was advertised for prophylactic use in all pregnancies (see Fig. 1.1).

In the following decades, cases of a rare clear-cell adenocarcinoma (CCA) of the vagina were reported in young women whose mothers had taken DES during pregnancy. This type of vaginal cancer had previously occurred mainly in post-menopausal women and the new cases (with a median age of 19 years, range 15–29 years) alerted researchers to an association with DES, although exposure to the medicine had occurred many years prior to diagnosis of the adverse event (Goodman et al. 2011). The full story of DES was reviewed in the New England Journal of Medicine in 2011, 40 years after the issue was first reported in this journal (Goodman et al. 2011).

In Box 1.2 I have included a powerful personal testimony from Elizabeth Claire Hooper who discovered she was a "DES baby". It is a humbling and instructive story, which I hope will place women at the centre of all our efforts to prevent such tragedies happening again.

Box 1.2

It was my birthday and the phone was ringing. I expected it to be birthday greetings from a friend; instead, it was a nurse from the university health clinic. In an indifferent voice, she informed me that I had advanced cervical cancer and needed to seek treatment immediately. I quickly scheduled an appointment with a gynecologist for a second opinion; the second opinion was dire. The doctor flatly said I had both breast and cervical cancer. I desperately sought a third opinion from another OB/GYN. He examined me and told me that I did not have cancer, but I was a "DES Baby." Fortunately, I had found a gynecologist who is an expert in DES exposure. I was relieved to not have cancer, but the ramifications of being a DES Baby didn't fully sink into my consciousness at that moment.

Diethylstilbestrol (DES) is a synthetic form of estrogen that was prescribed to pregnant women in the United States from the 1940s through the early 1970s to prevent premature labor, miscarriage, and other potential complications of pregnancy; it was also used to "dry up" a mother's lactation during the time in which American women were inculcated with the idea that "formula" was superior to breast milk. DES was still being used in Europe into the late 1970s. By one estimate, DES was prescribed to six million women worldwide, even though a clinical study done in 1953 concluded the drug did not prevent miscarriages.

DES is a potent carcinogen. Pregnant or nursing women who took the drug have higher risks of certain cancers; this carcinogen passes from generation to generation with no end in sight at present. As a DES Baby, it would be difficult for me to have biological children; and if I did so, that child and all my descendants would still suffer from the increased risks of cancers and of DES-related deformities.

(continued)

Box 1.2 (continued)

I am lucky that I have not yet developed any DES-related cancers. I am lucky that my DES-related deformities are internal, not external. However, I'm not so fortunate in that this has been a "pre-existing condition," and that I have had to pay "out of pocket" for all the required, extra cancer screenings. Ironically, miscarriages (and infertility) are common among those women who were the progeny of mothers exposed to DES.

Few class action lawsuits against the pharmaceutical companies that created and supplied this drug have been successful. To paraphrase one judge, when ruling against a "DES Baby" class action lawsuit, we wouldn't want to stymie the pharmaceutical industry's right to innovation.

Elizabeth Claire Hooper **May 2014**

Overview of This Book

In this section I will summarise key points from each chapter and identify some important matters for further consideration. One aim is to highlight issues to compel you to read more in each of the 18 chapters, which have been written by expert authors from around the world. I have also added my own comments on specific issues – some of which may be viewed as controversial, but one purpose of this book is to provoke discussion on some of the more difficult issues associated with medicines for women. A further aim of this summary is to consolidate the huge amount of information provided – to bring the book together as a whole and to highlight the important themes.

Medicines for Women is divided into three parts: first, issues relating to women's exposure to medicines and considerations for particular subgroups of women are discussed; second, specific groups of medicines for women are reviewed; and in the third part different perspectives on women's medicines are presented. I have also identified some interesting (and often alarming) facts and figures from the 18 chapters and these are presented in Table 1.1.

Part I: Women's Exposure to Medicines and Consideration of Special Sub-populations

Examination of the effect of sex differences on the phases of drug disposition is an appropriate way to begin to understand how women's exposure to medicines may differ from men's. In Chap. 2, Drs Emmanuel Fadiran and Lei Zhang from the US Food and Drug Administration (FDA) examine sex differences in pharmacokinetics and consider how these may impact on the safety of medicines in women.