Drug utilization studies in pregnancy
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Chapter 7

OVULATION-INDUCING DRUGS
A DRUG UTILIZATION AND RISK STUDY IN THE DUTCH POPULATION


This chapter has been published as article in the International Journal of Risk and Safety in Medicine, 1992;3:99-112. Article is reprinted with permission of the Publisher
ABSTRACT

This study describes the use of the ovulation-stimulating drugs clomiphene, human Chorionic Gonadotropin (hCG) and human Menopausal Gonadotropin (hMG) in a representative sample of a population of Dutch women in the child-bearing age group. Clomiphene or hMG/hCG are seldom used alone. A considerable percentage of the women received at least four different ovulation-inducing and related drugs during the observation period of two years. Thirty percent of the women who used clomiphene were treated for 6 or more cycles. These findings argue for a relative “overuse” and “misuse of clomiphene. Buserelin, a drug not registered for the indication ovulation induction in The Netherlands but used in in vitro fertilization (IVF) programs as inhibitors of pituitary gonadotropine production, was nevertheless prescribed to 38% of the hMG/hCG users and to 11% of the clomiphene users. Our study indicates that, though the potential risks of congenital malformations due to clomiphene are difficult to assess, they may be considerable; this, and the fact that different ovulation-inducing drugs are used together with clomiphene, emphasizes the need for post-marketing surveillance.

INTRODUCTION

Since the ultimate risk of a drug for the human foetus is difficult to detect prior to introduction to the market, it is generally stated that the side effects of drugs for the unborn child are detected only by experiments of nature. Drug utilization studies may help to document the frequency of drug use in a population at risk and may in combination with studies on the occurrence of congenital birth defects give more insight into the frequency of drug related congenital abnormalities. Such registration studies clearly are warranted for drugs used during the first trimester of pregnancy but also for drugs that may frequently be indicated shortly before pregnancy, especially when their influence continues after conception. Such studies are in particular welcomed if no alternative drugs for that indication are available.

One such drug is clomiphene, an ovulation-inducing agent with a structure related to that of diethylstilbestrol. Its half-life is approx. 5 days and metabolites have been demonstrated in blood samples on day 22 of the cycle (after ingestion on days 5–9) and in faeces up to six weeks after administration. Its ability to stimulate ovulation and thus to enhance the chance for fertilization and a following gestation is well established. Teratogenic effects have been reported in the rat. Clomiphene taken just before conception could have a teratogenic effect because its metabolites may still be present during early embryonic development. In the years 1973–1978 several cases of neural tube defects (NTD) were reported in children whose mothers had been treated with clomiphene to induce ovulation. Recently published data from three birth defects registries and two obstetric clinics confirmed the association between ovulation induction and NTD. These studies indicate that the relative risk is between 2 and 3. Due to the small number of women involved in
these studies no conclusive evidence is as yet available but more extensive work may provide us with the data needed. Cornel et al. therefore stress the importance of post-marketing surveillance studies that include prospective follow-up of a large number of pregnancies after ovulation induction to estimate the relative risk of neural tube defects.22

Adverse effects on the developing foetus associated with the use of ovulation-stimulating drugs may not be limited to neural tube defects. An Australian group found an association with neuroectodermal tumours.23 They report on 2 neuroblastomas and 1 medulloblastoma in 3 children born after in vitro fertilization (IVF), all from the first cohort of 604 IVF livebirths. The normal annual incidence rates in Australia are 1.0 and 0.4 per 100,000 children for neuroblastoma and medulloblastoma respectively. A further two patients were conceived after ovulation induction with clomiphene and artificial insemination.

Any suspicion that drugs which stimulate ovulation and may be present in early pregnancy have teratogenic effects, creates an urgent need for thorough studies to describe and quantify these suspected risks. A possible obstacle to such studies could be concomitant drug use, in particular use of other ovulation-inducing drugs, since it is increasingly difficult to identify any causal relation with an individual drug when increasing numbers of different drugs have been used. It is therefore important to investigate the intensity of co-medication in patients using ovulation-stimulating drugs. Such studies also may indicate the degree of excessive prescription and therefore the unnecessary risks to which women and unborn children are exposed.

We previously showed the reliability of drug utilization data that can be obtained from pharmacy records.24 Especially when drug use has to be studied in a large population, pharmacy records offer the best tool to obtain optimal information.25 In this study we will report on the frequency and intensity of the use of clomiphene and of other ovulation-inducing drugs in a representative sample of a population of Dutch women in the child-bearing age group to better define the group that is at risk for the development of severe birth defects.

METHODS

Forty-two pharmacies in The Netherlands that were equipped with a computerized registration system (Pharmacom) were asked to cooperate in a search for patient exposure to ovulation-inducing drugs. All agreed to participate in the study, thus offering us an insight into the blinded pharmacy records of the patients registered at these pharmacies. The pharmacies were widely distributed over the country and included establishments from both urban and rural areas. The pharmacies covered a total population of approximately 524,417 persons, which is approximately 3.4% of the entire Dutch population. The age distribution of the population under study was no different from the age distribution of the Dutch population as a whole.26 The population studied included approximately 83,907 females 20–40 years of age.
Of this population, all women of fertile age who received at least one prescription for the ovulation-inducing drug clomiphene (ATC code G03GB02) in the period from January 1st 1989 to June 30th 1989 were included in the study as clomiphene users (n=250). Another 84 women were included because they received human chorionic gonadotropin (hCG) and/or human menopausal gonadotropin (hMG) without clomiphene during this inclusion period of 6 months.

The drug histories of these 334 (250 + 84) women were studied from the pharmacy records during a follow-up period of two years, i.e. from January 1st 1989 to December 31th 1990. The follow-up period was thus at least 18 months for each woman. We collected data on all drugs (both the ovulation-inducing agents and other prescriptions) that were dispensed to these women. For each of these prescriptions we were informed as to the date of dispensing, the total amount of the drug dispensed and the daily dose. Drugs were classified according to the Anatomical Therapeutical Chemical (ATC) classification. In our analysis we will discuss separately the group of 250 women selected on the use of clomiphene and the group of 84 women selected on the use of hMG/hCG.

Table 2A  The number (and percentage) of women using ovulation stimulating and related drugs during a two years follow-up.

<table>
<thead>
<tr>
<th>Generic name</th>
<th>ATC code</th>
<th>Clomiphene-users</th>
<th>hMG/hCG-users</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n=250</td>
<td>n=84</td>
</tr>
<tr>
<td>Clomiphene</td>
<td>G03GB02</td>
<td>250 (100)</td>
<td>15 (18)</td>
</tr>
<tr>
<td>Human chorion gonadotropin (hCG)</td>
<td>G03GA01</td>
<td>112 (45)</td>
<td>74 (88)</td>
</tr>
<tr>
<td>Human menopausal gonadotropin (hMG)</td>
<td>G03GA02</td>
<td>66 (26)</td>
<td>67 (80)</td>
</tr>
<tr>
<td>Progestins</td>
<td>G03D</td>
<td>117 (47)</td>
<td>42 (50)</td>
</tr>
<tr>
<td>Busereline</td>
<td>L02AE01</td>
<td>28 (11)</td>
<td>32 (38)</td>
</tr>
<tr>
<td>Urofollitropine</td>
<td>G03GA04</td>
<td>16 (6)</td>
<td>17 (20)</td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>G02CB01</td>
<td>25 (10)</td>
<td>6 (7)</td>
</tr>
<tr>
<td>Gonadoreline</td>
<td>H01CA01</td>
<td>5 (2)</td>
<td>4 (5)</td>
</tr>
<tr>
<td>Estrogens</td>
<td>G03C</td>
<td>34 (14)</td>
<td>11 (13)</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>H02AB</td>
<td>15 (6)</td>
<td>7 (8)</td>
</tr>
<tr>
<td>Primosistone</td>
<td>G03FA01</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Cyproteron</td>
<td>G03HB</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Danazol</td>
<td>G03XA01</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Hormones antagonist</td>
<td>L02BA01</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>NSAID’s</td>
<td>M01A</td>
<td>68 (27)</td>
<td>31 (37)</td>
</tr>
<tr>
<td>Analgesics</td>
<td>N02B</td>
<td>62 (25)</td>
<td>28 (33)</td>
</tr>
</tbody>
</table>

Clomiphene-users: women who received at least one prescription of clomiphene in the first 6 months of 1989
hMG/hCG-users: women who received at least one prescription of hMG and/or hCG but no clomiphene in the first 6 months of 1989.

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Clomiphene is generally used in a dose of 50 mg per day during 5 days of the early follicular phase of the menstrual cycle, and repeated if necessary during subsequent cycles. We therefore defined the standard treatment as consisting of 250mg clomiphene. We calculated, based upon the number of prescriptions prescribed to a woman during the follow-up period, how many cycles of treatment of clomiphene she had used, and in what dose, and whether she had also used ovulation related drugs at the same time or in a later cycle (without clomiphene). Drugs or hormones related to ovulation include, alongside clomiphene, all forms of medication used in ovulation induction regimens (see Table 2A).

Table 2B  The number (and percentage) of women using ovulation stimulating and related drugs during a two years follow-up.

<table>
<thead>
<tr>
<th>Generic name</th>
<th>ATC code</th>
<th>Clomiphene n=170</th>
<th>hMG/hCG n=84</th>
<th>Clom+ hMG/hCG n=80</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clomiphene</td>
<td>G03GB02</td>
<td>170 (100)</td>
<td>15 (18)</td>
<td>80 (100)</td>
</tr>
<tr>
<td>Human chorion gonadotropin (hCG)</td>
<td>G03GA01</td>
<td>33 (19)</td>
<td>74 (88)</td>
<td>79 (99)</td>
</tr>
<tr>
<td>Human menopausal gonadotropin (hMG)</td>
<td>G03GA02</td>
<td>19 (11)</td>
<td>67 (80)</td>
<td>47 (59)</td>
</tr>
<tr>
<td>Progestins</td>
<td>G03D</td>
<td>74 (44)</td>
<td>42 (50)</td>
<td>39 (49)</td>
</tr>
<tr>
<td>Busereline</td>
<td>L02AE01</td>
<td>9 (5)</td>
<td>32 (38)</td>
<td>23 (29)</td>
</tr>
<tr>
<td>Urofollotropine</td>
<td>G03GA04</td>
<td>5 (3)</td>
<td>17 (20)</td>
<td>11 (14)</td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>G02CB01</td>
<td>15 (9)</td>
<td>6 (7)</td>
<td>8 (10)</td>
</tr>
<tr>
<td>Gonadoreline</td>
<td>H01CA01</td>
<td>4 (2)</td>
<td>4 (5)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Estrogens</td>
<td>G03C</td>
<td>20 (12)</td>
<td>11 (13)</td>
<td>14 (18)</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>H02AB</td>
<td>11 (6)</td>
<td>7 (8)</td>
<td>4 (5)</td>
</tr>
<tr>
<td>Primosistone</td>
<td>G03FA01</td>
<td>9 (5)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cyproteron</td>
<td>G03HB</td>
<td>4 (2)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Danazol</td>
<td>G03XA01</td>
<td>4 (2)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Hormones antagonist</td>
<td>L02BA01</td>
<td>3</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>NSAID’s</td>
<td>M01A</td>
<td>51 (30)</td>
<td>31 (37)</td>
<td>17 (21)</td>
</tr>
<tr>
<td>Analgesics</td>
<td>N02B</td>
<td>44 (26)</td>
<td>28 (33)</td>
<td>18 (23)</td>
</tr>
</tbody>
</table>

Clomiphene-users: women who received at least one prescription of clomiphene in the first 6 months of 1989
hMG/hCG-users: women who received at least one prescription of hMG and/or hCG but no clomiphene in the first 6 months of 1989.
Clomiphene + hMG/hCG-users: women who received at least one prescription of clomiphene and one prescription of hMG and/or hCG in the first 6 months of 1989.

Where the information on a prescription regarding drug dose or duration of the treatment was incomplete, we calculated the number of cycles of treatment of clomiphene per prescription according to the following approach:

* if the prescribed dose was less than 250 mg, the number of cycles of treatment was defined as 1;
if the daily dose was indicated, the number of treated cycles was calculated as 
the total prescribed dose divided by the daily dose divided by 5. However, 
if a further prescription followed within this calculated period, the number of 
cycles of treatment was corrected to fit in the period between the two prescrip-
tions;

* if the information on the daily dose was lacking, the number of cycles of treat-
ment was calculated as the number of days in between this and the following 
clomiphene prescription divided by 28 (the number of days of one cycle), with 
a minimum of 250 mg per cycle of treatment;

* in the remaining cases the number of cycles of treatment was calculated ac-
cording to the previous prescriptions of that particular woman; where there 
were no previous prescriptions we assumed that 250 mg had been used per 
cycle of treatment.

In 701 out of the 797 clomiphene prescriptions, the daily dose indicated was ac-
cepted, in 46 out of the 797 the daily dose on the pharmacy record was changed 
and in 50 out of 797 the daily dose was lacking. The results of these calculations for 
the 797 clomiphene prescriptions are presented in Table 1.

<table>
<thead>
<tr>
<th>total number of cycles per presc.</th>
<th>number of prescriptions (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>493 (62)</td>
</tr>
<tr>
<td>2</td>
<td>143 (18)</td>
</tr>
<tr>
<td>3</td>
<td>86 (11)</td>
</tr>
<tr>
<td>&gt;3</td>
<td>75 (9)</td>
</tr>
</tbody>
</table>

mean 1.76

Results are presented as the number and percentage of the women exposed to a 
specified drug or class of drugs and as mean ± standard deviation. The Chi-squared 
test was used to compare proportions between groups. Student’s t-test was used for 
comparison of means, applying the paired and unpaired method when appropriate. 
Differences were considered to be significant if the p value was <0.05. DBase-IV 
and SPSS-programmes were used for analyses.

RESULTS

As pointed out above, 250 + 84 out of approximately 84,000, or approximately 4 
(±0.25) per 1,000 women in the age group 20–40 years had received at least one 
prescription of clomiphene, hCG or hMG during the first 6 months of 1989. The
mean age of the women studied was higher than the mean maternal age at the time of birth in The Netherlands (30.5 versus 27.8 years; \( p<0.0001 \)). Since we have only information on the date of the use of the ovulation-inducing drug and not on the date of any birth which may have followed, we should, for an optimal comparison of the age, reduce the maternal age by 9/12 (0.75) year. The age distribution of the women is shown in Figure 1.

![Figure 1](image.png)

**Figure 1** The age distribution of the women treated with ovulation-inducing drugs (bars) in The Netherlands and of Dutch mothers as a whole (line) (age at delivery).

The 250 clomiphene users and the 84 hMG/hCG users overall received a mean number of 8.7 and 9.4 different drugs respectively, during the period of follow-up. The number of different ovulation-inducing and related drugs taken was significantly lower in the clomiphene group \( (2.9 \pm 1.7) \) as compared to the hMG/hCG group \( (3.5 \pm 1.7) \) (\( p=0.002 \)). Figure 2 shows the percentage of women in both the clomiphene and the hMG/hCG group who used one or more different ovulation-inducing or related drugs. Twenty-three of clomiphene users and 13 percent of hMG/hCG users received only one ovulation-inducing drug during the two year follow-up period. A considerable percentage of the women (30% of clomiphene users and 50% of hMG/hCG users) received at least four different ovulation-inducing and related drugs during the observation period. The age of the women is not related to the number of different ovulation-inducing and related drugs used. Table 2A shows the number and percentage of women receiving the different individual ovulation-inducing and related drugs. Besides the three drugs under study, progestins (norethisterone, dydrogesterone, medroxyprogesterone and lynestrenol) were prescribed most frequently in both groups. The use of urofollotropine (so called pure FSH) and busereline was higher for the hMG/hCG users as compared
Figure 2 Percentage of women of both the clomiphene (dark bars) (n=250) and the hMG/hCG group (light bars) (n=84) that used one or more different ovulation-inducing or related drugs.

to the clomiphene users. This difference in use is even more evident when the clomiphene users are divided into clomiphene only users (n=170) and those who used both clomiphene and hMG/hCG (n=80) (Table 2B). The use of bromocriptine, gonadoreline, and estrogens was similar in both groups. We next sought to determine whether women who received not only clomiphene but also other ovulation-inducing drugs, used the latter drug in the same cycle in which clomiphene was given or in a following cycle during which no clomiphene was taken. Only busereline and bromocriptine were used more frequent in a later cycle (without clomiphene), whereas the other drugs were used as frequently in the same as in a following cycle.

Our study group much more commonly received non-steroidal antiinflammatory drugs and analgesics than did a comparable group of pregnant women. The NSAID'S most frequently used were diclofenac, ibuprofen and naproxen; paracetamol in combination with coffeeine was the most prominent of the analgesics.

The mean number (± SD) of cycles of treatment of clomiphene in the 250 women selected for its use was 5.5 (± 4.4) per women. Thirty percent of the women received clomiphene for more than 6 cycles of treatment (Fig. 3). There is no difference in the mean number of different ovulation related drugs during the two years follow-up period between the women who were treated for only one cycle of treatment and those who were treated for more cycles of treatments (Fig. 3).

The prescribed dose per cycle of treatment increased during each subsequent cycle from 1.6 (i.e. 1.6 times the standard dose of 250 mg) in the first cycle of treatment to 1.8 from the eighth cycle of treatment onwards (p<0.05) (Fig. 4), whereas the
Figure 3  Percentage of the 250 women who received clomiphene for one or more cycles of treatment (bars) and the mean number of different ovulation related drugs used in women who were treated for one or more cycles (line).

Figure 4  The prescribed dose per serial number of the cycle of treatment (bars) and the mean number of different ovulation related drugs prescribed in the same cycle (line).

The number of different ovulation related drugs during the two years period did not increase during consecutive treatment cycles (Fig. 4).
DISCUSSION

As pointed out above, 334 out of approximately 84,000 women, or 4 (±0.25) per 1,000 women in the age group of 20–40 years were found to use at least one prescription for an ovulation-inducing drug during a six month period. This could be an underestimation because our primary selection of drugs included only the use of clomiphene, hCG or hMG, and no other ovulation-stimulating drugs. We have no information on the number of women who conceived in the observation period and therefore we cannot indicate the frequency of earlier drug use in a pregnant population. We can however, make some assumptions. Firstly, the inclusion criterion for this study was the use of ovulation-stimulating drugs during a six month period. As the use of ovulation-inducing drugs usually does not last much longer than a few months, some 6 out of 1,000 women would be expected to use an ovulation-inducing drug in the course of a year. The proportion of women who become pregnant after the use of ovulation-inducing drugs is assessed at 30% (6). Assuming that this is correct, 1.8 (30% of 6 women) pregnancies after ovulation stimulation among 1,000 female inhabitants would be expected. The mean fertility rate for women aged 20–40 was in 1989 75 live births per 1,000 females. Thus 2.4% (1.8/75) of all pregnancies would be expected to originate after ovulation stimulation. In previous studies in pregnant women in The Netherlands (1988 and 1990), we found that 1.4 and 2.7% respectively of pregnant women had received one or more of these prescriptions prior to pregnancy.29,30 Our present estimation is in the same range and we have the impression that the use of ovulation-inducing drugs is increasing. The total number of live births and stillbirths in The Netherlands in 1990 was 199,104. Even using the above conservative estimate, approximately 4800 of these children would have been born after ovulation stimulation. The expected number of cases of NTD attributable to ovulation stimulation would be 7 to 14, assuming a baseline prevalence of 1/700 [31] and a relative risk of 2–3. The expected number of neuroectodermal tumours attributable to ovulation-inducing drugs to be expected within some years following birth would be,24 assuming a 1/200 attributable risk. Both these numbers would relate to a birth cohort of one year. When setting these figures alongside the 25 Softenon (thalidomide) babies who were born in the early sixties in The Netherlands,32 the possible magnitude of the problem is evident. Feed-back data from birth defect registries should render it possible to establish the proportion of all cases of neural tube defects in which clomiphene has been involved.

The present study population appeared significantly older than the general population of pregnant women in The Netherlands. This is not surprising, since it usually takes some time before a couple seek medical advice for infertility and because it again will take some time before the physician starts to use such drugs. It also indicates however, that one should be cautious in concluding that the use of such drugs is related to a higher risk of congenital abnormalities, since the incidence of chromosomal malformations has also been found to increase in an older age group.33,34 This age-related risk was correctly taken into account in a recent study.
showing an increased risk of birth defects during the use of clomiphene.\(^17\)

Clomiphene is used as monotherapy in appropriately selected anovulatory women in whom ovulatory dysfunction with adequate serum estrogen concentrations has been demonstrated. Some gynaecologists prescribe in addition corticosteroids in the case of overproduction of adrenal androgens, or use of bromocriptin when moderate hyperprolactinemia (co)exists. The primary use of hMG/hCG is substitution of deficient pituitary gonadotropin release, nowadays mainly because of primary pituitary disease. However, our analysis shows that clomiphene is often followed by hMG/hCG as a secondary drug for induction of ovulation. Also hCG is often used in the same cycle as clomiphene, or in a following cycle without clomiphene treatment. It is reasonable to assume that in medical practice one starts ‘blind’ with the use of clomiphene. The number of other ovulation related drugs during the two-years follow-up period does not increase with the number of cycles of treatment: women who were only treated for one or two cycles with clomiphene used as many different ovulation related drugs as those who were treated for more than 6 cycles. Besides the three drugs under study (clomiphene, hCG, and hMG) the most commonly prescribed hormones or hormone related drugs were progestins, busereline and urofollotropine. Progestins are used to determine whether estrogen concentrations are sufficiently high to merit the use of clomiphene as an ovulation-inducing drug. Busereline and urofollotropine were frequently used in the group of hMG/hCG users. In the Netherlands, busereline is registered for the treatment of disseminated hormone dependent carcinoma of the prostate.\(^35\) It has a relatively short half-life and therefore it has been adopted as a means of creating hypogonadotrophic state, thereby facilitating follicular stimulation with hMG, especially in “controlled” ovarian hyperstimulation with hMG/hCG as currently used in in vitro fertilization protocols. This accounts for its prescription to users of ovulation-inducing drugs, and its use should thus be considered as experimental. Nevertheless, it was prescribed to 11% of the clomiphene users and to 38% of the hMG/hCG users, probably as part of IVF treatment. Interestingly, non-steroidal antiinflammatory drugs and analgesics were also frequently used. The percentage of women who used non-steroidal antiinflammatory drugs is much higher (27.2 and 36.9%) than that found in a study on pharmacy records of pregnant subjects.\(^24\) In that study only 2.8% of the women used a drug from this category in the 6-month period prior to pregnancy (which is a period comparable to that used in the women in the present study). Most probably this higher use of nonsteroidal antiinflammatory drugs is the consequence of ovulatory or premenstrual pain secondary to the use of the ovulation-inducing drug. We should keep in mind the fact that possible interactions between clomiphene and such nonsteroidal antiinflammatory drugs, other ovulation-stimulating drugs or other drugs frequently used under these conditions, might contribute to the suspected teratogenic effects of clomiphene.

Thirty percent of the women who used clomiphene were treated for 6 or more cycles. It is well known from the literature that the effectiveness of ovulation induction decreases significantly after three cycles of treatment. The recommended maximum number of cycles of treatment of clomiphene is, according to the litera-
ture, three to six. Our calculation of the total number of cycles of treatment on the one hand could be an overestimation because in the case of a missing daily dose a prescription was assumed to be meant for the whole period until a new prescription followed. On the other hand an underestimation of the total number of treated cycles is likely, since we did not know how many women had already used clomiphene before the date of January 1, 1989. If the total number of cycles of treatment were to be an overestimation, due to the missing daily dose, than the total dose clomiphene per cycle is an underestimation. The mean dose of clomiphene per cycle in this study is in agreement with the dose recommended (50 to 100 mg during 5 days). We found in the consecutive cycles a significant increase in the dose of clomiphene used per treated cycle. These findings taken together suggest a relative "overuse" or "misuse" of clomiphene in terms of duration of therapy.

Many women treated with drugs for ovulation induction are past the optimum age for child bearing: 10% were older than 38. Notwithstanding the urgency of the indication for ovulation induction, i.e.: long-standing involuntary infertility, one might consider whether the cumulative risk (age and clomiphene-related) does not outweigh the benefits on the therapy. In a recent review in which the risks of ovulation induction are evaluated, the need was suggested to limit the number of women exposed unnecessarily. Our findings underline the need for post-marketing surveillance studies; the results show a clear discrepancy between the theoretical golden standard (notably as regards the number of cycles of treatment to be employed and the concomitant use of other drugs) and actual practice. The experimental use of some drugs is an additional justification for post-marketing surveillance. By combining drug utilization data obtained via pharmacies, which include not only the clomiphene and/or hMG/hCG prescriptions but also all concomitantly used drugs, with data from registries of congenital abnormalities one will be able to develop knowledge as to the teratogenic risk and safety of ovulation stimulation drugs.

REFERENCES