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ORIGINAL ARTICLE

Use of fertility drugs in Denmark 1973–1993

An analysis based on sale statistics

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Objectives. The increasing use of drugs for ovarian stimulation and the possibility of long-term risks has actualized a quantitative assessment of the use of such therapy. The aim of the study was to analyze the development in the sale of different types of drugs used for ovarian stimulation in Denmark during the last two decades.
Material. Sale statistics of clomiphene citrate, cyclophenile, human menopausal gonadotropin (hMG), mare menopausal gonadotropin (mMG) and human chorionic gonadotropin (hCG) in Denmark 1973–1993.
Methods. The number of defined daily doses (DDD) was calculated for each product group. On given assumptions the number of cycles of different treatment regimens and the number of treated women was calculated.
Results. The sale has increased almost exponentially throughout the last two decades: Clomiphene citrate 11 fold, hMG 30 fold, and hCG 5 fold. Today, among women 15–44 years old, the estimated incidence rate of women treated with clomiphene alone is about 2.7/1,000/year, and the incidence rate of women treated with clomiphene/hCG and hMG/hCG account for about 3.1/1,000/year and 1.9/1,000/year, respectively.
Conclusion. Any study concerning short- and long-term effects of ovarian stimulation have to consider this secular trend.

Key words: chorionic gonadotropin; clomiphene citrate; Denmark; fertility drugs; menopausal gonadotropin; sale statistics

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Stimulation of follicular growth in anovulatory women with clomiphene citrate has been available in Denmark since the beginning of the 1960's. At that time human menopausal gonadotropin (hMG) also came into use, followed a few years later by human chorionic gonadotropin (hCG).

Until the early eighties, induction of ovulation was restricted to anovulatory women with polycystic ovarian syndrome, hypothalamic anovulation or hyperprolactinemia.

From the early eighties, 'superstimulation', which means a desired overstimulation of the ovaries, has been used in many infertile women, either in combination with *in vitro* fertilization (IVF) or intrauterine insemination.

The increasing use of these regimens has actualized an assessment of short- and long-term benefits and risks, in particular any changed risk of ovarian cancer (1–3). As a basis for such epidemiological analyses, the aim of this study was to achieve detailed knowledge of the use of different types of drugs used for ovarian stimulation in Denmark through the last two decades, and to estimate the number of women treated with different medical regimens.

Abbreviations:
hMG: human menopausal gonadotropin; hCG: human chorionic gonadotropin; DDD: defined daily doses; IVF: *in vitro* fertilization; ADD: adjusted daily doses.

Material and methods

We obtained permission from all Danish pharmaceutical companies to use the internal sale statistics of the Danish Drug Statistics concerning preparations for induction of ovulation. In 1993, where parallel imported drugs became available in Denmark, these data were supplemented with the sale from the most important parallel importer, as these figures are not included in the statistics from the Danish Drug Statistics.

Calculation of sale

For each drug, the sale statistics provided information about content per tablet/ampoule, number of tablets/ampoules per package and the number of packages sold.

A Defined Daily Dose (DDD) is internationally defined as the dose a patient typically is prescribed within one day. For each year and each preparation, the number of DDD was calculated (Table I) and the number of DDD was summarized for each product (=group of preparations) (Fig. 1).

A minor part of hCG is used by veterinarians. The veterinary use of hCG was estimated from the number of treated animals and veterinary gonadotropin (Gorolone) sold. Gorolone has been available in Denmark from 1979. In Denmark approximately 1–1.5% of 800,000 cows have been treated annually throughout the last 25 years, corresponding to approximately 10,000 treatments/year, each demanding 3,000 IE hCG or Gorolone. The sale of Gorolone has, since 1979, accounted for about 1,000 treatments per year. Thus the veterinary use of hCG was assessed as 10,000×3,000 IE hCG per year before 1979 and 9,000×3,000 IE hCG after 1979. This veterinary use was taken away from the sale statistics in the present analysis in order to assess only human applications of hCG.

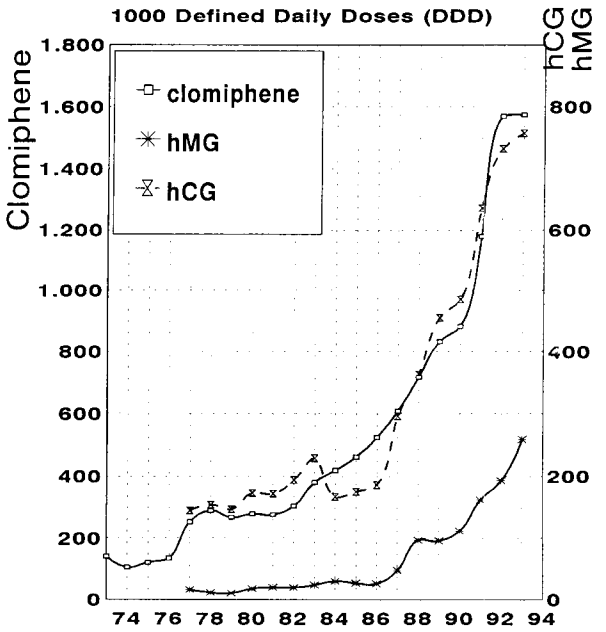

Fig. 1. The sale of three main products for infertility treatment in Denmark 1973–1993. Sale indicated according to the defined daily doses (DDD).

Cycles of treatment

From the DDD, the number of cycles of treatment was calculated on the following assumptions:

* A cycle is of 30 days.
* The use is equivalent to the sale.

Table I. Preparations in use for female infertility. Types, defined daily doses (DDD) and estimated daily doses (ADD) according to the practice in Denmark

	hCG	hMG	mMG	Clomiphene	Cyclophenile
Medicine group Unit	G03G A01 IE	G03G A02 IE	G03G A03 IE	G03G B mg	G03G mg
Content per tablet/ampul	1500 3000 5000	75 150	1500	50	100
Typical dose per cycle in Denmark	7500	450 or 900 or 1200	4500×5	100×5	400×10
Defined daily dose (DDD)	7500/30=250	900/30=30	4500×5/30=750	50×5/30=9	400×10/30=133
Adjusted daily dose (ADD)	250	15, 30 and 40	750	100×5/30=17	133
Commercial names	Physex Pregnyl Profasi	Humegon Pergonal	Antex	Clomivid Pergotime	Sexovid

As various doses and stimulatory regimens have been used in Denmark, an *adjusted daily dose* (ADD) was calculated according to typical Danish regimens, which were based on the following treatment assumptions (Table I):

* Clomiphene citrate: 500 mg per cycle (100 mg in 5 days), corresponding an ADD of 17 mg.
* Cyclophenile (available 1977–1981): 4000 mg per cycle (400 mg in 10 days), corresponding an ADD=DDD of 133 mg. In the following Figures, this sale was added to the sale figures of Clomiphene citrate.
* HMG: *Before 1989:* 900 IE per cycle (typically 75IE for 12 days), corresponding to an ADD of 30 IE. *After 1989:* Half of the patients as before 1989 (900 IE/cycle), half of the patients with 1,500 IE/cycle (typically 150 IE for 10 days), corresponding to an average ADD of 40 IE.
* MMG (Antex®, available 1977–1991): 4500 IE for 5 days per cycle. DDD=750 IE.
* HCG: 7500 IE per cycle. ADD=DDD=250 IE.

Women on different treatment regimens

The sale statistics do not give any information about the number of women treated or the occurrence of different treatment regimens. In order to provide an estimate of the number of treated women, the above mentioned doses were assumed, and the following treatment regimens considered:

* *HCG alone:* 10% of the hCG was given without preceding treatment with clomiphene citrate or hMG, e.g. in connection with intrauterine insemination.
* *HMG & hCG:* Treatment with hMG is always followed by 7500 IE of hCG.
* *Clomiphene citrate, hMG & hCG* treatment has been used mainly since 1986, and was characterized by clomiphene citrate 100 mg for 5 days, 450 IE hMG, followed by 7500 IE of hCG. We assume that since 1986 approximately 500 women have received this combined treatment per year.
* *Clomiphene citrate and hCG:* The remaining hCG is given with clomiphene citrate with 7500 IE per cycle.
* *Clomiphene citrate alone:* The remaining clomiphene citrate is given alone.

These treatment regimens were laid down after discussions with colleagues in fertility departments and clinics in Denmark, as no empirical data are available. They therefore represent no more than a qualified guess. In the calculation of the number of treated women it was assumed that each woman is treated on average for four cycles. The number of women in Denmark between 15 and 44 years has been stable during the study period, and accounts about 1.1 mio.

Results

Fig. 1 illustrates the development in the sale of the three main groups of infertility products: Clomiphene citrate, hMG, and hCG. It was not possible to achieve knowledge about the sale of hMG and hCG during the first four years of the study period (1973–1976). Calculations of different treatment regimens were, therefore, restricted to the period 1977–1993.

The sale of tablets (clomiphene citrate and cyclophenile) increased more than 11 times during the 21 year study period. The hMG sale increased slowly until 1986, from which time the sale increased 13 times or with on average 44% per year through the last seven years. HCG exhibited a more moderate increase of 5.2 times during the 16-year period, or on average about 16% per year.

The corresponding number of cycles indicates roughly the distribution of the three main groups of preparations according to the prescription practice in Denmark (Fig. 2). The total number of

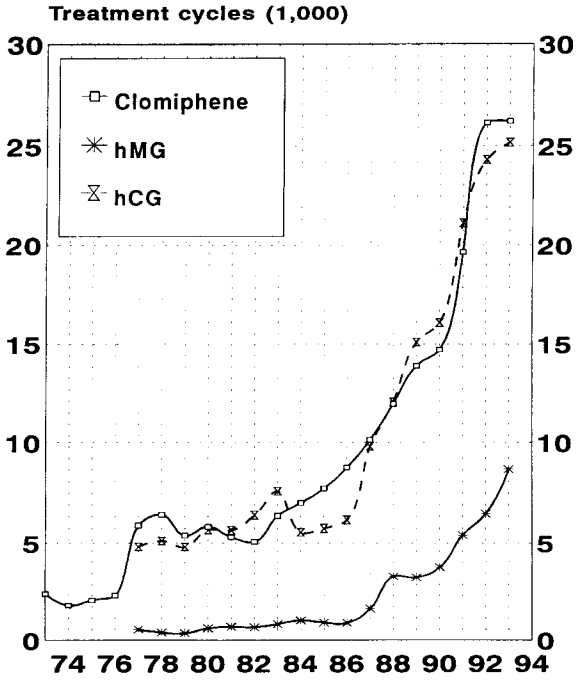

Fig. 2. The sale of three main products for infertility treatments in Denmark 1973–1993. The sale indicated in the number of treatment cycles, calculated according to an adjusted daily dose (ADD) reflecting the practice in Denmark.

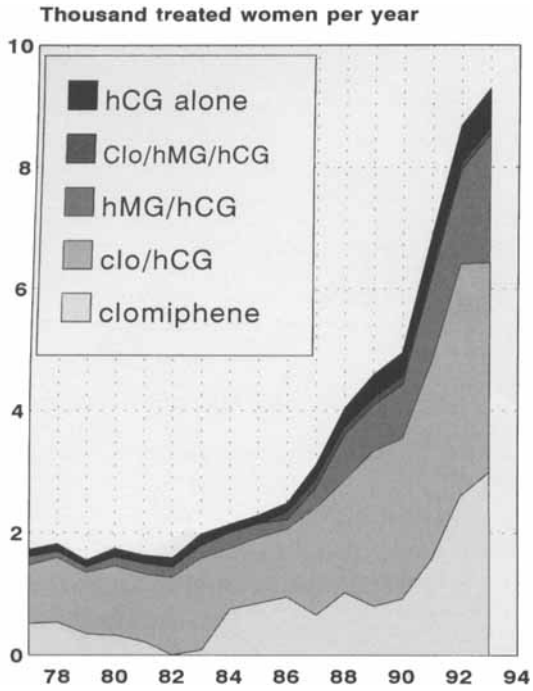

Fig. 3. Annual estimated number of women on different infertility treatment regimens in Denmark 1977-1993. These figures are based on several assumptions, see text.

treatment cycles increased 5.3 fold during the period 1977–1993.

Finally, Fig. 3 indicates the estimated number of women on different treatment regimens throughout the period 1977–1993. Although these data were based on many uncertain assumptions, the nearly exponentially increasing trend in the different treatment regiments appears. According to these figures, and assuming that each woman on the average receives four treatment cycles, the number of women treated in 1993 will be as follows: 3,000 women are treated with clomiphene per year, 3,400 are annually treated with clomiphene and hCG, and 2,100 are on a hMG/hCG combined regimen. These figures correspond an annual incidence rate of these regimens of 2.7, 3.1 and 1.9 per 1,000 women 15–44 years, respectively.

Discussion

The present statistics are considered to represent a valid estimate of the sale, and thereby of the use of the different types of drugs for ovarian stimulation in Denmark. The principal uncertainty was the veterinary use of hCG. As this use in all circumstances only applies to the hCG, and as its proportion of the total hCG sale was low, even major changes in the estimated veterinary use will not change the figures substantially.

The estimated number of treatment cycles (Fig. 2) implies more uncertainty. Although other assumptions could have changed the absolute number of cycles in the different years, the rapidly increasing trend would not be altered.

The calculations of the number of women treated with different regimens, depends firstly on the assumption that each woman on average is treated through four cycles, secondly on specific assumption according to the different combined regimens. These assumptions were difficult to assess, as practice has changed throughout the last 20 years, and because of a significant regional variability during the study period. These secular changes and regional variations reflect both the lack of official recommendations, and the dramatic difference in inter-individual responses to these drugs. The suggested trends, nevertheless, represent our best estimate of the development in the use of these drugs in Denmark.

The low number of women treated solely with tablets during 1982–1983 may be a consequence of some women being treated with only 50 mg clomiphene×5/cycle.

The increased use of clomiphene and hMG may reflect that the drugs are used on wider indications than previously. Today 'superovulation' is not only used for IVF and intrauterine insemination with husband's semen, but also at intrauterine insemination with donor sperm. Secondly, we have some reports indicating an increased seeking of infertility treatment among couples with these problems. Thus Templeton et al. reported an increased secular trend in these consultations in Scotland (4). In Denmark Rachootin & Olsen investigated the seeking practice among a representative sample of 709 women 25–45 years old in 1979 (5). They reported that less than of one third of primary infecund women had sought hospital care, and that 44% had consulted their general practitioner. Unfortunately, we do not have any later data, but probably these percentages are higher today. Thirdly, there is a trend towards the use of GnRH agonists and hMG in a long protocol with larger doses of hMG per stimulation cycle (6–8). And, finally, it is possible, but so far undocumented, that there might have been a real increase in the prevalence of female infertility (9).

It has been difficult to relate the trend in drug use in Denmark with the development in other countries, due to the lack of publications on this issue. A recent publication by Wysowski (10) reports a linearly 1.9 fold increase in the number of clomiphene citrate prescriptions in the USA during the same two decades. This development differs significantly from the nearly exponential increase in Denmark. In 1991, about 731,000 prescriptions of clomiphene citrate was registered in USA, or

approximately 14.6 per thousand women 15–44 years of age. The corresponding Danish figure was 18 clomiphene cycles/1000 women 15–44 years. Anticipating a prescription of clomiphene citrate of between one and two cycles in the USA, the consumption in the two countries is comparable.

The short-term effects of the fertility drugs are the well known direct side effects of the drugs and the risk of hyperstimulation and multiple pregnancies. Less is known about the long-term effects. As a consequence of the increasing use of these drugs, it is now important to clarify also the long-term effects. During the last few years there have been several reports of ovarian cancer after induction of ovulation (1–3, 11–18). The majority of these reports are casuistic (11–18). Three case-control studies reported conflicting results (1–3). This may reflect the fact that different types of ovarian pathology demand medical stimulation to achieve pregnancy, at the same time imply an increased risk of malignant transformation, or in other words a selection phenomenon (19–21).

The results from the present study stress the importance of including also adjustments for the significant secular trend in the occurrence of infertility treatment in any epidemiological attempts to clarify the long-term effects of this medical treatment.

References

1. Whittemore AS, Harris R, Itnyre J et al. Characteristics relating to ovarian cancer risk: Collaborative analysis of 12 US case-control studies. Am J Epidemiol 1992; 136: 1184–1203.
2. Rossing MA, Daling JR, Weiss NS, Moore DE, Self SG. Ovarian tumors in a cohort of infertile women. N Engl J Med 1994; 331: 771–6.
3. Franceschi S, La Vecchia C, Negri E et al. Fertility drugs and risk of epithelial ovarian cancer in Italy. Human Reprod 1994; 9: 1673–5.
4. Templeton A, Fraser C, Thompson B. Infertility – epidemiology and referral practice. Human Reprod 1991; 6: 1391–4.
5. Rachootin P, Olsen J. Social selection in seeking medical care for reduced fecundity among women in Denmark. J Epid Comm Health 1981; 35: 262–4.
6. Vaclavinsler BL. Induction of ovulation: historical aspects. Clin Obstet Gynecol 1990; 4: 473–89.
7. Blacker CM. Ovulation stimulation and induction. Reprod Endocrin 1992; 21: 57–84.
8. Hughes EG, Fedorkon DM, Daya S, Sagle MA, Van de Koppel P, Collins JA. The routine use of GnRH agonists prior to IVF and GIFT: a metaanalysis of randomized controlled trials. Fertil Steril 1992; 58: 888–96.
9. Healy DL, Trounson AO, Andersen AN. Female infertility: causes and treatment. Lancet 1994; 343: 1539–44.
10. Wysowski DK. Use of fertility drugs in the United States, 1973 through 1991. Fertil Steril 1993; 60: 1096–8.
11. Kulkarni R, McGarry JM. Follicular stimulation and ovarian cancer. BMJ 1989; 299: 70.
12. Casagrande JT, Pike MC, Ross RK, Louie EW, Roy S, Henderson BE. 'Incesssant ovulation' and ovarian cancer. Lancet 1979; vii: 170.
13. Carter ME, Joyce DN. Ovarian carcinoma in a patient hyperstimulated by gonadotropin therapy for in vitro fertilization: A case report. J In Vitro Fert Embryo Transf 1987; 4: 126.
14. Atlas M, Menczer J. Massive hyperstimulation and borderline carcinoma of the ovary. A possible association. Acta Obstet Gynecol Scand 1982; 61: 261.
15. Dietl J. Ovulation and ovarian cancer. Lancet 1991; 338: 445.
16. Nijman HW, Burger CW, Baak JPA, Schats R, Vermorken JB, Kenemans P. Borderline malignancy of the ovary and controlled hyperstimulation, a report of 2 cases. Eur J Cancer 1992; 28A: 1971.
17. Goldberg GL, Runowicz CD. Ovarian carcinoma of low malignant potential, infertility, and induction of ovulation – Is there a link ? Am J Obstet Gynecol 1992; 166: 853.
18. Willemsen W, Kruitwagen R, Bastiaans B, Hanselaar T, Rolland R. Ovarian stimulation and granulosa-cell tumour. Lancet 1993; 341: 986.
19. Balasch J, Barri PN. Follicular stimulation and ovarian cancer. Hum Reprod 1993; 8: 990–6.
20. Cohen J, Forman R, Harlap S et al. IFFS expert group report on the Whittermore study related to the risk of ovarian cancer associated with the use of infertility agents. Human Reprod 1993; 8: 996–9.
21. Spirtas, R, Kaufman SC, Alexander NJ. Fertility drugs and ovarian cancer: red alert or red herring? Fertil Steril 1993; 59: 291–3.

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