

A Study on Utilization of Oral Contraceptives in the City of Zagreb (2008–2010)

Ana Zelić-Kerep¹, Danijela Štimac^{2,3}, Sanja Ožić², Krešimir Živković⁴ and Nikica Živković⁵

¹ Kutina health Center, General Practice Office, Kutina, Croatia

² »Dr. Andrija Štampar« Institute of Public Health, Zagreb, Croatia

³ University of Zagreb, School of Medicine, Department of Social Medicine and Organization of Health care, Zagreb, Croatia

⁴ University of Zagreb, University Hospital »Sveti Duh«, Department of Gynaecology and Obstetrics, Zagreb, Croatia

⁵ Šibenik-Knin County General Hospital, Department of Gynaecology and Obstetrics, Šibenik, Croatia

ABSTRACT

Main aim of this study is to quantify and analyze the utilization and utilization trends of oral hormonal contraceptives in the City of Zagreb, 2008–2010, and to propose potential interventions, if necessary. Data gathered from Zagreb pharmacies were assessed by Anatomical Therapeutic Chemical Classification of drugs and Daily Defined Dose methodology. An alarming decrease in total utilization of hormonal contraceptives by 76% from 2008–2009 was found as the main result of this study. A major decrease by 95.5% in utilization of G03AB04 subgroup, sequential combined oral contraceptives, was noted in the year 2009. The subgroup G03AC0, progesterone-only pill group, showed a stable trend, and it became the most utilized subgroup in 2010, due to the decrease in utilization of both fixed and sequential combined oral contraceptives. Utilization of oral contraceptives in Croatia is not regulated adequately, since such dynamics in utilization can occur unnoticed. Measures need to take place in order to improve this situation. Proposed measures include organized farmacovigilance, prescription based on guidelines, and strict screening for risk factors in women seeking oral contraception. More research is required in Croatia to understand the pattern of utilization of hormonal contraceptives and to find the true cause of decrease in utilization of oral contraceptives.

Key words: oral contraceptives, safety, drug, pharmaceutical epidemiology, drug utilizations, ATC/DDD methodology, public health

Introduction

Hormonal contraception is an effective, easy to administer way of preventing unplanned pregnancies, thus being very eligible for young females who want to achieve effective family planning. The first contraceptive revolution began in the 1950s in the USA, with the invention of hormonal contraceptives and this method was first approved in the USA in 1960. Nowadays about 100 million women all over the world are using this birth control method¹. Although this kind of contraception is widely used, and strongly promoted as an effective and safe birth control method, it is not without flaws. Hormonal contraceptives may cause several side-effects, including deep venous thrombosis, acne, mood swings, and can also increase the risk of breast and cervical cancer, and many other problems^{2,3}. However, since the data available in Croatia have not been adequately evaluated, the true situ-

ation within the Croatian female population is not known. Therefore, potential issues cannot be dealt with effectively. The utilization of oral contraceptives in Croatia is still controversial, and comprehension regarding utilization trends of oral contraceptives in Croatia is incomplete. Even though the G03 group of drugs (sexual hormones) is accountable for two thirds of utilization of the entire G group (drugs affecting the urogenital system and sexual hormones), these data are not adequately assessed⁴. The capital of Croatia, City of Zagreb was chosen as a representative sample for this study, since it accounts for 18% of the Croatian population and 43% of the Croatian health resources, and therefore accurately represents Croatian trends⁵. Nowadays, it is completely unacceptable to have such a poor insight into the utilization of hormonal contraceptives, therefore, it is absolutely

necessary to conduct this study, as a first step towards identifying potential concerns, as well as improving this important aspect of public health.

Research Objectives

Aims of this study are as follows:

1) To quantify the utilization of oral contraceptives in the City of Zagreb, the capital of Croatia, between the years 2008 and 2010, using the Anatomical-Therapeutic-Chemical drug classification (ATC), and the defined daily doses unit (DDD), or in other words, the ATC/DDD methodology as a standard method of drug utilization monitoring

2) To assess the trend in utilization of oral contraceptives in the City of Zagreb, during the abovementioned time span, using ATC/DDD methodology.

Methods

Data on the utilization of hormonal contraceptives (ATC group G03) in the City of Zagreb were collected between 2008 and 2010. They were acquired from Zagreb’s pharmacies that had recorded the data based on individual prescriptions. All the drugs have been classified according to the ATC system. The data acquired have been used to calculate the DDD by using the indexes of 2008, 2009 and 2010⁶⁻⁸. ATC/DDD methodology is generally recognized as a method for drug utilization quantification.

Results

According to the ATC classification, hormonal contraceptives are classified into these three subgroups of current interest: G03AA (fixed combinations), G03AB (sequential combinations) and G03AC (single-hormone contraceptives).

Table 1 represents the total utilization of hormonal contraceptives in the City of Zagreb expressed in DDDs, from 2008 – 2010. Subgroup G03AC03 accounts for the entire utilization of G03AC group of drugs, so this subgroup was taken into account for this study. There is an

TABLE 2
UTILIZATION OF ORAL CONTRACEPTIVES IN THE CITY OF ZAGREB, 2008–2010, EXPRESSED IN DDDs, TOTAL SUM OF FIXED AND SEQUENTIAL COMBINED ORAL CONTRACEPTIVES AND PROGESTERONE-ONLY CONTRACEPTIVES.

ATC code	2008	2009	2010
G03AA	14.389	16.016	13.109
G03AB	835.386	56.949	44.671
G03AC03	231.400	221.000	205.400

Legend: ATC – Anatomical-Therapeutic-Chemical Classification, G03AA – combined oral contraceptives, fixed combinations, G03AB – combined oral contraceptives, sequential combinations, G03AC03 – progesterone – only contraceptives

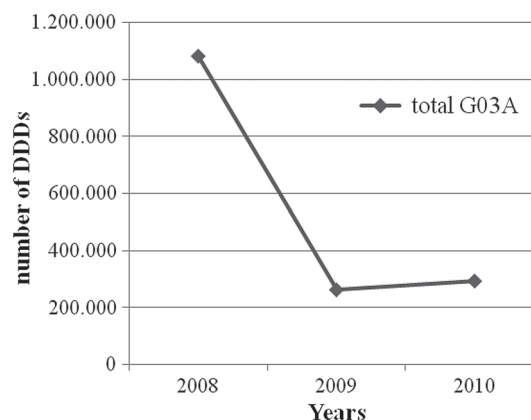


Fig. 1. The overall decrease in the total utilization of oral contraceptives (G03A) in the City of Zagreb, expressed in the number of Defined Daily Doses (DDDs), 2008–2010.

overall decrease in the utilization of all observed subgroups. The total number of DDDs decreases between years 2008 and 2009 by 76%. When comparing years 2009 and 2010, a small increase in utilization expressed in DDDs by 10.5% is noted. The subgroup G03AB04 accounts for the majority of hormonal contraceptives utilization through the entire study period, i.e. it makes up for 52% of total utilization of all subgroups, from 2008–2010. However, the subgroup G03AB04 accounted for 73.7% of overall G03A group utilization in 2008. A major decrease by 95.5% in utilization of G03AB04 subgroup expressed

TABLE 1
UTILIZATION OF ORAL CONTRACEPTIVES IN THE CITY OF ZAGREB, 2008–2010, EXPRESSED IN DDDs

ATC code	2008	2009	2010	Total per study period
G03AA	13.353	15.206	12.504	41.063
G03AA13	1.036	810	605	2.451
G03AB	39.122	20.801	14.655	74.578
G03AB04	796.264	36.148	30.016	862.428
G03AC03	231.400	221.000	205.400	657.800
Total G03A	1.081.175	263.180	293.965	1.638.320

Legend: ATC – Anatomical-Therapeutic-Chemical classification, G03AA, G03AA13 – combined oral contraceptives, fixed combinations, G03AB, G03AB04 – combined oral contraceptives, sequential combinations, G03AC03 – progesterone – only contraceptives

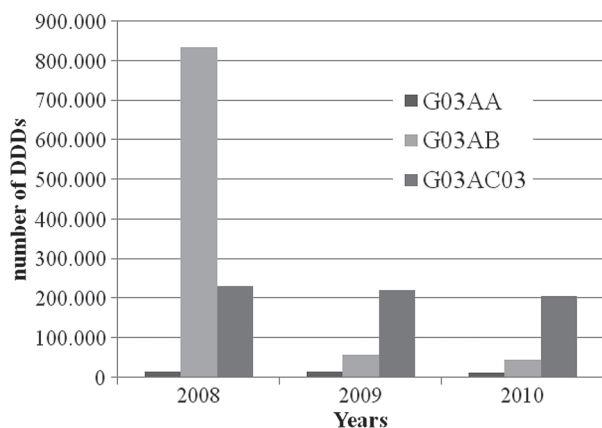


Fig. 2. The ratios between the utilization of subgroups G03AA (fixed combinations), G03AB (sequential combinations) and G03AC03 (progesterone-only contraceptives) of oral contraceptives expressed in the number of DDDs (Daily Defined Doses) in the City of Zagreb, during the study period.

in DDDs was noted in the year 2009 and in 2010 by another 17%. Subgroup G03AA13 also showed a decrease in utilization during the observed time span by 42%. Meanwhile, the subgroup G03AC03 has a stable trend, showing a minimal decrease in the utilization expressed in DDDs, by 12% during the study period. Table 2 shows the ratio between each subgroup to one another, showing that the group G03AC03 becomes the most utilized subgroup in 2009, due to the dramatic decrease in utilization of other subgroups.

Figures 1 and 2 depict above described data. Figure 1 graphically shows the overall decrease in the total utilization of hormonal contraceptives, while Figure 2 shows the ratio between the utilization of subgroups during the study period.

Discussion

As already stated, it was known before that G03 subgroup (hormonal contraceptives) accounts for two thirds of entire G group (drugs affecting urogenital system and sexual hormones) utilization in Croatia. Serious assessment of this data was lacking, making appropriate public health or otherwise interventions impossible. The problem lays in the fact that the competent institutions do not carefully analyze the utilization of hormonal contraceptives. For example, Croatian Institute for Health Insurance does not have most of the registered oral contraceptives on their drug lists, both basic and additional, so that institution does not keep track of utilization of the majority of oral contraceptives in use. Also, Agency for Medicinal Products and Medical Devices of Croatia keeps a rough record of utilization, not adequate for finer analyses. It is important to stress that oral contraceptives in Croatia are not *over-the-counter* drugs, and only gynecological specialists prescribe them.

Time span from 2008–2010 was chosen as a result of the pursuit to avoid display of vast unnecessary data, but

still to have the most recent data. According to Croatian Health Service Yearbook 2008, the most common contraceptives prescribed were oral contraceptives (73.1%)⁹. From 2008 to 2009 the number of visits to primary health care's gynecologists for prescribing hormonal contraceptives dropped by 20%¹⁰. In 2010 the number of visits to primary health care gynecologists for prescribing hormonal contraceptives dropped by a mere 0.4%, indicating stabilization¹¹. The results presented in this paper show a major decrease in the utilization of hormonal contraceptives, by 76% from 2008–2009. The number of abortions dropped by 2%, from 2008–2009, so abortion as a form of contraception did not cause the decrease in utilization of hormonal contraceptives¹⁰. According to primary health care data, the prescription of all forms of contraception (oral, intrauterine, the diaphragm and other local forms) decreased by 30% from 2008–2009, and in 2010 dropped by another 24%. Namely, intrauterine form of contraception dropped by 23%, the usage of diaphragm by 61%, and other local forms of birth control by 39%, from 2008–2009^{12,13}. This indicates that this is not the case of another emerging form of contraception substituting hormonal contraception. It is clear that an event occurred in 2008, which could be associated with this dramatic decrease in utilization of hormonal contraceptives. This event could be the deaths by pulmonary embolism of a two young women as side-effects of hormonal contraception, widely promoted by the Croatian media. These unfortunate events were caused by a contraceptive »Yasmin«, of Bayer d.o.o., a combination of ethinyl-estradiol and drospirenone. After these unfortunate events took place, a safety profile check of the accused drug was conducted. It was found that all the women who suffered various major adverse effects, including abovementioned lethal ones, had other risk factors and the drug in fact was contraindicated for these women. The drug was declared to be very safe¹⁴. Even though, there are scientific researches showing contradictory, if not even opposite results. For example, in 2002 and 2003 some published articles suggest that this combined oral contraceptive is useful and recommendable, contributing to women's overall well-being, and some articles report transient ischemic attacks and thromboembolic events associated with Yasmin^{15,16}. The controversy remains the same in more recently published articles^{17,18}. But, it cannot be proven that these unfortunate events caused such dynamics in our data, it can only be guessed. For the time being, it is the only conclusion that can be made with any kind of certainty, since the media have a big impact on public opinion; hormonal contraception is not an exception. However, it is important to stress that the subgroup G03AB04 makes up for the majority of hormonal contraceptives utilization, and that the utilization of this subgroup decreased by 95.5%, from 2008 to 2009. G03AB04 is a code for hormonal contraceptives comprised of norethisterone, a second generation progestin, and oestrogen. This combination of hormones was the most prescribed combination of all hormonal contraceptives, till 2009. In 2009 the most prescribed hormonal contraceptives were the ones in the subgroup G03AC03, the single hormone

oral contraceptives, containing only progestin, possibly out of fear of oestrogen exacerbating adverse effects.

Since population is still a vitally important policy area in developing countries, such as Croatia, trends in fertility are an important focus in public health. The so-called »second demographic transition«, taking place in developing and developed countries, Croatia included, characterized by declining age at first intercourse and increasing age at first childbirth, creates an extended interval during which people are at risk of unintended pregnancy¹⁹. According to »World fertility patterns 2009«, a publication of United Nations' Department of Economic and Social Affairs, Population Division, the mean age at childbearing in Croatia shifted 1970–2006 from 26 years of age, to 28 and a half²⁰. Taking that into account, with the data showing a decline by 76%, in just one year, of hormonal contraception utilization creates an alarming image of Croatian public health situation, regarding family planning and population policy. The result of this study itself, the decrease in hormonal contraceptives utilization by such a great percentage, which was unnoticed by responsible institutions, is a serious implication for action regarding this matter in Croatia.

When it comes to adherence of hormonal contraception utilization to current trends and the latest findings regarding safety and efficacy, there are no studies looking into that matter. So far, it is known that the risk of venous thrombosis in current users of combined oral contraceptives decreases with duration of use and decreasing oestrogen dose. Combined oral contraceptives containing the same dose of oestrogen with desogestrel, gestodene, or drospirenone were associated with a significantly higher risk of venous thrombosis than oral contraceptives with levonorgestrel^{21,22}. Progestogen only pills and hormone releasing intrauterine devices were not associated with any increased risk of venous thrombosis according to a study in 2009²³. From that point of view, it can be considered a positive trend, this decline in utilization of combined hormonal contraceptives, and a stable trend in single hormone utilization. Especially since oestrogen-containing pills cannot be prescribed to women who smoke, and it is known that there are numerous female smokers in Croatia, 21.7%, according to the Health for All Database²⁴. An extensive meta-analysis in 2011 concludes that in order to exclude the relation between myocardial infarction and utilization of progestogen-only contraceptives more research is needed, since current observational studies suggesting there is no increase in the risk of myocardial infarction are based on very limited

data²⁵. Also, low-dose combined oral contraceptives are well tolerated by most women and most mild side-effects tend to improve over time, when it comes to observing intermediate outcomes in combined oral contraceptives²⁶.

The prescription of hormonal contraception in Croatia is clearly out of control, even though concise guidelines exist. A better implementation of these guidelines could improve the state of hormonal contraception in Croatia. It is important for gynecologists who prescribe hormonal contraception to know exactly which conditions represent an unacceptable health risk, and even more important, which do not. Their prescriptions should be based on concise, already existing guidelines, to eliminate any irrational fear of unwanted events²⁷. All women seeking hormonal contraception should be vigorously screened for major and minor risk factors for arterial and venous diseases²⁸. Other proposed measures include a better organized pharmacovigilance, i.e. all adverse effects should be regularly noted and analyzed. The most important measure that needs to take place is an organized cooperation between the gynaecologists prescribing these drugs, responsible institutions and patients themselves. The data gathered needs to be analyzed continuously and consequentially.

Certain progress is visible in the developed world regarding hormonal contraception, meanwhile in Croatia there is no awareness about it in the public or in the health service. Currently, efforts are being made to improve the risk-to-benefit ratio of oral contraception by investigating the possibility of introducing new, natural oestrogens and investigating new progestins. New molecular methods are being used to discover potential genetic and proteomic targets for contraception²⁹.

Conclusion

This is the only study investigating this matter using ATC/DDD methodology, the only methodology qualified to assess drug utilization in an objective manner. It is of highest importance to investigate the true reason for such utilization dynamics, especially to find if this is in correlation with emergent data suggesting a higher risk of thromboembolism and other major adverse effects in relation to new hormonal contraceptives. In order to achieve the maximum of quality in health services providing contraception in Croatia results of this study should be taken into account and proposed measures implemented rapidly.

REFERENCES

1. HARRISON PF, ROSENFELD A, Contraceptive Research and Development-Looking to the Future (National Academy Press, Washington, 1996).
2. BERGENDAL A, ODLIND V, PERSSON I, KIELER H, Acta Obstet Gynecol Scand, 88 (2009) 261.
3. SHULMAN LP, Am J Obstet Gynecol, 205 (2011) 9.
4. ŠTIMAC D, Odnos izvanbolničke potrošnje lijekova u Gradu Zagrebu od 2001. do 2005. godine i regulatornih mjera. MS thesis. In Croat (University of Zagreb, Zagreb, 2008).
5. CROATIAN BUREAU OF STATISTICS, accessed 20.4.2012. Available from:

6. ANATOMICAL THERAPEUTIC CHEMICAL (ATC) Classification Index with Defined Daily Doses (DDDs). January 2008. Oslo: (WHO Collaborating Centre for Drug Statistics Methodology, 2008).
7. ANATOMICAL THERAPEUTIC CHEMICAL (ATC) Classification Index with Defined Daily Doses (DDDs). January 2009. Oslo: (WHO Collaborating Centre for Drug Statistics Methodology, 2009).
8. ANATOMICAL THERAPEUTIC CHEMICAL (ATC) Classification Index with Defined Daily Doses (DDDs). January 2010. Oslo: (WHO Collaborating

- Centre for Drug Statistics Methodology, 2010). — 9. HZJZ. Croatian National Institute of Public Health: List of Drugs. Official Gazette 2009, accessed 16.4.2012. Available from: URL: http://www.hzjz.hr/publikacije/hzs_ljetopis/Ljetopis_Yearbook_HR_2009.pdf. — 10. HZJZ. Croatian National Institute of Public Health: List of Drugs. Official Gazette 2010, accessed 16.4.2012. Available from: URL: http://www.hzjz.hr/publikacije/hzs_ljetopis/Ljetopis_Yearbook_HR_2010.pdf. — 11. HZJZ. Croatian National Institute of Public Health: List of Drugs. Official Gazette 2011, accessed 16.4.2012. Available from: URL: http://www.hzjz.hr/publikacije/hzs_ljetopis/Ljetopis_Yearbook_HR_2011.pdf. — 12. ŠTIMAC D, POLIĆ-VIŽINTIN M, Health condition of population and health care in 2009 (Institute of Public Health »Dr. Andrija Štampar«, Zagreb, 2010.). — 13. ŠTIMAC D, POLIĆ-VIŽINTIN M, Health condition of population and health care in 2010 (Institute of Public Health »Dr. Andrija Štampar«, Zagreb, 2011.). — 14. AGENCY FOR MEDICINAL PRODUCTS AND MEDICAL DEVICES OF CROATIA. Statement of the Agency for Medicinal Products and Medical Devices of Croatia on adverse effects reports of drugs in Croatia in 2008, accessed 20.4.2012. Available from: URL: http://www.almp.hr/pdf/publikacije/Izvjesce_o_nuspojavnima_2008.pdf. — 15. KEAM SJ, WAGSTAFF AJ, Treat Endocrinol. 2 (2003) 49. — 16. VAYÁ A, MIRA Y, FERRANDO F, AZNAR J, GARCÍA-FUSTER MJ, Thromb Res. 112 (2003) 121. — 17. KELLY S, DAVIES E, FEARNES S, MCKINNON C, CARTER R, GERLINGER C, SMITHERS A, Clin Drug Investig, 30 (2010) 25. DOI: 10.2165/11535450-000000000-00000. — 18. OO TH, South Med J, 102 (2009) 985. — 19. ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS, Consensus views arising from the 49th RCOG Study Group, accessed 16.4.2011. Available from: URL: <http://www.rcog.org.uk/files/rcogcorp/uploadedfiles/StudyGroupConsensusViewsContraception.pdf>. — 20. UNITED NATIONS, DEPARTMENT OF ECONOMIC AND SOCIAL AFFAIRS, POPULATION DIVISION. World fertility patterns, accessed 1.5.2012. Available from: URL: <http://www.un.org/esa/population/publications/worldfertility2009/worldfertility2009.htm>. — 21. GRONICH N, LAVI I, RENNERT, CMAJ, 183(2011) 1319. — 22. KEMMEREN JM, ALGRA A, GROBBEE DE, BMJ, 323(2001) 131. — 23. LIDEGAARD Ø, LØKKEGAARD E, SVENDSEN AL, AGGER C, BMJ, 339 (2009) 2890. DOI: 10.1136/bmj.b2890. — 24. WORLD HEALTH ORGANIZATION, Health for all database, accessed 20.4.2012. Available from: URL: <http://data.euro.who.int/tobacco/Default.aspx?TabID=2404>. — 25. CHAKHTOURA Z, CANONICO M, GOMPEL A, SCARABIN PY, PLU-BUREAU G, J Clin Endocrinol Metab, 96 (2011) 1169. — 26. INTERNATIONAL PLANNED PARENTHOOD FEDERATION, IPPF Medical Bulletin – Volume 36 accessed 1.5.2012. Available from: URL: <http://www.ippf.org/en/Resources/Medical/Volume+36+Number+5+October+2002.htm>. — 27. NO AUTHORS LISTED, Committee opinion no. 505: understanding and using the U.S. Medical Eligibility Criteria For Contraceptive Use 2010. Obstet Gynecol, 118 (2011) 754. — 28. WEBBERLEY H, MANN M, Curr Obstet Gynecol, 16 (2006) 21. — 29. BURKMAN R, BELL C, SERFAT D, Contraception, 84 (2011) 19.

A. Zelić-Kerep

Kutina health Center, General Practice Office, A.G. Matoša 32, 44320 Kutina, Croatia
e-mail: zelic_ana@yahoo.com

ISTRAŽIVANJE POTROŠNJE ORALNIH HORMONSKIH KONTRACEPTIVA U GRADU ZAGREBU, 2008–2010 GODINE

SAŽETAK

Glavni cilj ove studije je kvantificirati i analizirati potrošnju i trendove potrošnje oralnih hormonskih kontraceptiva u Gradu Zagrebu, 2008–2010 godine, te predložiti potencijalne intervencije, ako se pokaže potrebnim. Podaci skupljeni iz ljekarni Grada Zagreba obrađeni su metodologijom Anatomsko-Terapijsko-Kemijske klasifikacije (ATK) i Definirane Dnevne Doze (DDD). Alarman pad ukupne potrošnje hormonskih kontraceptiva od 76% zabilježen je od u razdoblju od 2008. godine do 2009. godine. U 2009. godini došlo je do pada potrošnje kontraceptiva podgrupe G03AB04, sekvencijskih kombiniranih oralnih kontraceptiva, za čak 95.5%. Podgrupa G03AC0, oralni hormonski kontraceptivi koji sadrže samo progesteron, pokazuje stabilan trend potrošnje te je postala najprepisivanija podgrupa oralnih hormonskih kontraceptiva u 2010. godini. To je djelomično rezultat pada potrošnje fiksni i sekvencijskih kombinacija oralnih hormonskih kontraceptiva. Potrošnja oralnih hormonskih kontraceptiva u Hrvatskoj nije adekvatno regulirana, što pokazuje ovakva dinamika potrošnje, koja je dosada bila nezapažena. Potrebne su intervencije da se ovakva situacija poboljša. Predložene mjere uključuju organiziranu farmakovigilanciju, propisivanje temeljeno na smjernicama i obavezno detaljno traženje faktora rizika u žena koje žele oralnu hormonsku kontracepciju. Također, potrebna su dodatna istraživanja da bi se u potpunosti moglo shvatiti kretanje potrošnje hormonskih kontraceptiva, te da bi se pronašao pravi uzrok padu potrošnje oralnih hormonskih kontraceptiva u Hrvatskoj.