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Medication before and during pregnancy: data from Generation XXI birth cohort

Dissertation presented to obtain a Master´s degree in Public Health

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Porto, 2013

Acknowledgements

I am very grateful to all those who in some way or other accompanied me throughout my personal and academic journey, supporting me through all the steps in my experience and achievements as a person and an academic.

I thank my family for transmitting important values that have made me the person that I am today. A special thanks to my parents, grandparents, aunts, uncles and cousins. To my mother, who was always by my side, in the good and bad moments and for having encouraged me and for believing in me.

We live in an increasingly competitive and material society and despite that, my friends have always showed me the true meaning of friendship. They were always there for me in my time of need. I also thank those who have been with me since my childhood and have never abandoned me and those that I met at university.

I thank my supervisor Professor Doutor José Henrique Barros who shared his knowledge in public health and epidemiology, for his assistance in analyzing the data presented and reviewing the work.

I also express my gratitude to my co-supervisor Mestre Sofia Correia for all the help she gave me and for guiding me through all investigation steps. Without her, this work would not have been possible.

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List of Acronyms

ADEC – Australian Drug Evaluation Committee

ASHP – American Society of Health-Systems Pharmacists

ATC – Anatomical Therapeutic Chemical Classification

CI – Confidence Interval

CMV – Cytomegalovirus

DES – Diethylstilbestrol

EphMRA – European Pharmaceutical Market Research Association

FASS – Swedish system

FDA – USA Food and Drug Administration

IMS – Internacional Medical Statistics

IQR – Interquartile range

INFARMED – Autoridade Nacional do Medicamento e Produtos de Saúde IP

OR – Odds Ratio

OTC – Over-the-counter

PT – Prontuário Terapêutico

PV – Pharmacovigilance

SD – Standard deviation

WHO – World Health Organization

Abstract

Introduction: Drug use during pregnancy should be carefully analysed in order to try to establish safe practice and avoid usage of dangerous substances. There is little or no evidence for safe use in pregnancy in relation to many habitually used drugs however, recent studies have shown elevated levels of drug usage among pregnant women.

Objective: To assess the prevalence of drug use before and during pregnancy and to estimate the maternal determinants of such use among mothers of the Generation XXI birth cohort.

Methods: The present study is based on the Generation XXI cohort, which included 8647 newborns, whose mothers (8495) were recruited at delivery from April 2005 to August 2006 in one of the five public maternity units that cover six municipalities of the metropolitan area of Porto, Portugal. Information on social and demographic characteristics, obstetric and gynecological history, lifestyles and current pregnancy events was obtained using a structured questionnaire during the hospital stay (24-72 hours after the delivery) by trained interviewers. Through this survey we were able to collect information regarding drug use three month before and during pregnancy. All the drugs were classified according to the Anatomical Therapeutic Chemical Classification System (ATC) from the World Health Organization (WHO) and US Food and Drug Administration (FDA) risk classification system. In order to classify the drugs according to the FDA we used Infarmed publications from December 2004 and August 2011.

Results: The prevalence of overall drug use before conception and during pregnancy was respectively 49.2% and 98.3%. In both time periods, 30.8% of women took drugs. Excluding supplements (ATC A11, A12 and B03), the prevalence of drug use before, during pregnancy and in both time periods decreased to 34.9%, 60.2% and 15.3%, respectively. Before pregnancy, 5537 drugs were reported by women while, during the pregnancy this number increased to 27775. In accordance with the ATC system classification the most common preconception drugs used were from category G and B (22.8% and 19.1% of women took at least one drug from these categories). During pregnancy, 95.4% of women reported having used drugs from category B, 66.4% from category A, 19.7% from category N and 16.4% from

category J. During pregnancy and according to the 2011 Infarmed publication (based on FDA classification system), drugs from category A and category B were used by 91.6% and 29.0% of women respectively. Category C was used by 18.9% of the women and categories D and X were taken by 8.7% and 0.2% of women respectively. When the 2004 Infarmed publication was used to classify the drugs, the percentage of use for category C and D decreased respectively to 9.1% and 6.8%. Category X remained the same in both publications. Before pregnancy and after adjusting the models, more educated women, primiparous women and those who had chronic diseases were more likely to have used drugs. Excluding supplements, the educational level and parity were no longer associated with drug use, however having reported chronic diseases remained associated in the same way as stated above. Women who lived with a partner were less likely to have used drugs, while those who had not planned the current pregnancy and had smoked before pregnancy were more likely to have used drugs. During pregnancy and after adjusting the models, the use of drugs was less likely to occur in less educated women, those who smoked before pregnancy and in those who were housewives or unemployed. Women, who chose private prenatal care, had more appointments and complications during pregnancy were more likely to have used drugs. After excluding supplements, women with chronic diseases and those who did not plan the current pregnancy were more likely to use drugs. The working condition and the health care system were no longer associated with drug use.

Conclusion: According to our findings, whether we include supplements or not, there is an evident tendency for a greater use of drugs during pregnancy when comparing with the three months before pregnancy. Drug use during pregnancy by women was very common; however, according to the FDA classification system the proportion of women who used drugs from category D and X was low. Before pregnancy, the use of drugs was associated with the existence of a chronic condition. The use of drugs prior to pregnancy was linked with better social profiles when the supplements were included, while when they were excluded, it was associated with worse profiles. During pregnancy, despite the universal use of medicines, similar patterns were observed. These studies are essential for creating prescription guidelines during pregnancy in order to improve medical care.

Resumo

Introdução: A utilização de medicamentos durante a gravidez deve ser analisada de forma cuidadosa, para estabelecer práticas seguras e evitar o uso de substâncias perigosas. Existe pouca ou nenhuma evidência clínica quanto à segurança da maioria dos medicamentos utilizados durante a gravidez contudo, estudos recentes demonstram prevalências elevadas de utilização.

Objetivo: Estimar a prevalência da utilização de medicamentos antes e durante a gravidez e identificar os determinantes maternos entre as mães da cohort de nascimentos Geração XXI.

Métodos: O presente estudo é baseado na cohort Geração XXI que inclui 8647 recém-nascidos, cujas mães (8945) foram recrutadas no momento do parto, entre abril 2005 e agosto 2006 numa das cinco unidades de maternidade que servem seis dos municípios da área metropolitana do Porto, norte de Portugal. Durante a hospitalização (24-72 horas pós-parto), através de um questionário estruturado e aplicado por entrevistadores treinados, foi recolhida informação relativa a características sociais e demográficas, historial obstétrico e ginecológico, estilos de vida e eventos ocorridos durante a gravidez. Através deste questionário foi também reunida informação relativa à utilização de medicamentos três meses antes e durante a gravidez. Todos os medicamentos foram classificados de acordo com a Anatomical Therapeutic Chemical Classification System (ATC) da World Health Organization (WHO) e com o sistema de classificação de risco da US Food and Drug Administration (FDA). Para classificar os medicamentos de acordo com o sistema de classificação da FDA foram utilizadas duas publicações do Infarmed, uma de dezembro de 2004 e outra de agosto de 2011.

Resultados: A prevalência de utilização de medicamentos três meses antes e durante a gravidez foi respetivamente, 49.2% e 98.3%. Em ambos os momentos, 30.8% das mulheres tomaram medicamentos. Excluindo os suplementos (ATC A11, A12 e B03), a prevalência de utilização de medicamentos antes, durante a gravidez e em ambos os momentos diminuiu, respetivamente para 34.9%, 60.2% e 15.3%. Antes da gravidez, foram declarados 5537 medicamentos pelas mulheres e durante a gravidez, este número aumentou para 27775. De acordo com o sistema de classificação ATC, os medicamentos mais utilizados antes da gravidez pertenciam às categorias G e B e foram utilizados por 22.8% e 19.1% das mulheres, respetivamente. Durante a gravidez, 95.4% das mulheres usaram medicamentos pertencentes

à categoria B, 66.4% à categoria A, 19.7% à categoria N e 16.4% à categoria J. Durante a gravidez e de acordo com a publicação do Infarmed de 2011 (baseada no sistema de classificação da FDA), medicamentos pertencentes às categorias A e B foram utilizados por 91.6% e 29.0% das mulheres, respetivamente. A categoria C foi utilizada por 18.9% das mulheres e as categorias D e X por 8.7% e 0.2%, respetivamente. Usando a publicação do Infarmed de 2004 para classificar os medicamentos, a percentagem de utilização das categorias C e D diminuiu, respetivamente para 9.1% e 6.8%. A categoria X permaneceu similar em ambas as publicações. Antes da gravidez e após ajustar os modelos, as mulheres mais escolarizadas, primiparas e as que declaram doenças crónicas tinham maior probabilidade de ter usado medicamentos. Excluindo os suplementos, a escolaridade e a paridade deixaram de estar associadas ao uso de medicamentos no entanto, ter declarado doenças crónicas permaneceu associado no mesmo sentido. Mulheres que moravam com companheiro eram menos propensas a usar medicamentos e as que não planearam a gravidez e fumaram antes da mesma tinham maior probabilidade de ter usado medicamentos. Durante a gravidez e após ajustar os modelos, o uso de medicamentos era menos provável ter ocorrido nas mulheres menos educadas, nas que fumaram antes da gravidez e nas que eram domésticas ou estavam desempregas. As mulheres que optaram pelo seguimento prenatal privado, as que tiveram um maior número de consultas e as que tiveram complicações durante a gravidez tinham maior probabilidade de ter usado medicamentos. Após exclusão dos suplementos, as mulheres que declaram doenças crónicas e as que não planearam a gravidez tinham maior probabilidade de ter tomado medicamentos. A condição laboral e o sistema de saúde deixaram de estar associados ao uso de medicamentos.

Conclusão: Independentemente da inclusão ou não dos suplementos existe uma tendência para um maior consumo de medicamentos durante a gravidez quando comparado com os três meses antes da gravidez. A utilização de medicamentos durante a gravidez foi muito frequente, no entanto, e de acordo com o sistema de classificação da FDA a proporção de mulheres que utilizou medicamentos pertencentes às categorias D e X foi baixa. Antes da gravidez, a utilização de medicamentos encontrava-se associada à existência de doenças crónicas. O uso de medicamentos antes da concepção encontrou-se associado a perfis sociais mais favoráveis, quando os suplementos estavam incluídos. Quando estes foram excluídos, associou-se a perfis sociais mais desfavoráveis. Na gravidez, e apesar de uso universal de medicamentos, padrões semelhantes foram verificados. Estes estudos são essenciais para elaborar guidelines de prescrição durante a gravidez, para melhorar práticas médicas.

1. Introduction

1.1 Human Teratology

Knowledge of the effects of prenatal exposure to pharmaceutical drugs and chemicals during pregnancy is crucial and prevents morbidity and mortality (1). The development stage of the intrauterine host is a main determinant of the outcome, as well as the nature and the concentration of the drug or chemical agent used (2).

A teratogen is usually characterized as an agent capable of inducing congenital abnormalities during the development period as a result of prenatal exposure (at any stage of embryogenesis). Agents include drugs and other chemicals. Physical forces (e.g. ionizing radiation or physical restraints like amniotic banding) or other factors such as maternal diseases can be considered to be such agents. Teratogenic maternal diseases which can be considered are conditions such as toxoplasmosis, cytomegalovirus (CMV), syphilis and others. Nonetheless, it is known that not all teratogenic agents have adverse fetal effects (1).

Congenital toxoplasmosis occurs from a transplacental diffusion. Assuming a normal immune system, this form of infection only takes place if the pregnant woman has a primary infection. A woman that has already been infected is usually not infected again because she should have an adequate immune response. Infection can lead to several manifestations in the foetus depending on the stage of the pregnancy when the woman acquires the infection however, hepatosplenomegaly, thrombocytopenia, microcephaly, convulsions, fever, and small-for-gestational-age newborns all suggest *Toxoplasma*. Risk of an infection in the first trimester is lower than the third, but severe congenital toxoplasmosis is associated with infection that occurs in early gestation. At birth, most neonates are asymptomatic. However, later in life deafness, mental retardation and learning difficulties can be detected (3, 4) .

CMV transmition from the mother to the foetus may occur in two different ways: through the placenta or during the birth via cervical secretions or blood. Infants may be also infected via breastfeeding. Women that already have been infected have a lower risk of transmition the virus to the foetus when comparing with women with a primary infection. One of the most frequent viral causes of congenital infections is CMV, which belongs to the herpes family, and it can be responsible for a hearing loss or deafness during childhood as well as contributing to other

neurodevelopmental disabilities in children (mental retardation, autism, learning disabilities, cerebral palsy, etc.). Motor disabilities and severe mental retardations may be easily identified during the first year of the children life however, mild mental retardations or learning disabilities became more evident only over the years. Hearing loss may occur during the first 6 years of a child's life in infections which are either symptomatic or asymptomatic during the neonatal period. Usually children with a symptomatic infection have hearing loss at an early age and with more severity than those with an asymptomatic infection. Visual damage and strabismus are also very usual among children with clinically apparent CMV infections and can be caused by chorioretinitis, pigmentary retinitis, macular scarring, optic atrophy or central cortical defects. Usually, infections in early pregnancy result in more severe sequels (5).

Syphilis infection during pregnancy can lead to adverse outcomes including miscarriage, stillbirth, nonimmunehy drops, prematurity, intrauterine growth restriction, and neonatal and infant death. Commonly, congenital syphilis is divided into two clinical conditions: early and late congenital syphilis. The first of these refers to the clinical symptoms that appear within 2 years of life and the second to the manifestations that occur after 2 years and usually near puberty. This is called late congenital syphilis. Early manifestations can be skin lesions, anaemia, splenomegaly and others. Late manifestations can involve frontal bossing, palatal deformation, dental dystrophies, nasal deformity and others. Transmition from the mother to the foetus may happen through placenta or at the delivery by the contact of the newborn with the genital lesion (6, 7).

At the beginning of the 1960's, thalidomide was the first drug that was showed to be a human teratogen. Of all the human teratogens, thalidomide represents the most infamous example of how such drugs might not be identified (1). In this particular case, the animal models were unsuccessful in identifying thalidomide as a dangerous substance when used during pregnancy, before it was introduced into the market (8). Thalidomide was not found to be very teratogenic in rodents, and screening tests did not show its high teratogenicity in humans and higher mammals (9, 10).

According to the human experience, thalidomide is one of the most potent teratogens ever discovered. It was used against nausea symptoms and in order to relieve morning sickness in pregnant women (8, 11). Thalidomide was introduced in West Germany in 1957, under the brand name Contergan and was subsequently licensed in 46 others European countries and in

Asia and African. After that, several pharmaceutical companies manufactured thalidomide in different concentrations and under different brand names (9). In Germany thalidomide was an over-the-counter drug (OTC), based on the safety claims of the producer (12).

Unfortunately, thalidomide was the cause of a huge number of severe malformations in humans; it was associated with different types of musculoskeletal defects, including the noted phocomelia: the structures of the hand and feet may be reduced into a single small digit, or may appear normal but stick out right from the trunk. Anomalies of the thumb (e.g. triphalangism), loss of hearing, anotia, microtia, renal malformations and congenital heart diseases have also been reported (1, 13, 14). There is evidence that thalidomide was only teratogenic from days 21 to 36 post-conception; when used in other time periods it seems to be harmless. There are some reported cases of women who took only one pill during the critical period and it was enough to cause damage (15). When compared with some teratogen agents, thalidomide differs because the dosage used seems not to be as relevant a factor as the time when the drug was used. This drug is quite rapidly hydrolysed and due to this short action time and the large number of women who used it, informative declarations could be ascertained. A huge number of women were able to say exactly when they took the drug and the number of pills used and a relation between the time of drug intake and resultant malformations could be established (16).

Recognition of the Thalidomide disaster in the 1960's as a cause of serious birth defects raised the awareness of women and healthcare professionals. After that, attention started to be given to the potential teratogenic risk of drugs especially during the first trimester of pregnancy (17, 18) and detailed risk stratification of drugs was emphasized (19) in order to reduce the use of some of them during pregnancy. Many preventative measures (such as rigorous toxicological tests and the creation of regulatory authorities) have been taken as a result of what happened (11, 20). Nevertheless, limiting the exercise of caution to the first 3 months of pregnancy is both unthinking and impossible because drugs can affect any stage of pre- or postnatal development and when a woman realizes that she is pregnant generally the organogenesis process has already begun (13). As a consequence the months leading up to the pregnancy are very important.

Diethylstilbestrol (DES), another important teratogenic drug, was used between the 1940's and the 1970's by pregnant women in order to prevent miscarriage, premature birth and related complications of pregnancy. DES is associated with adverse effects on reproductive tract in both male and female progeny. In males, these effects include epididymal cysts, microphallus,

cryptorchidism, and testicular hypoplasia and in females adenosis, clear-cell adenocarcinoma structural defects of the cervix, vagina, uterus and fallopian tube (21). After 1971, a relationship between the use of this hormone and the occurrence of clear-cell adenocarcinoma of the vagina in female offspring was established. The age of the women, at diagnosis, ranged from 7 to 28 years old (22). Some years later, in order to determine the effect of the exposure to DES, it was tested on pregnant mice (23).

It is a universal principle to avoid drug exposure especially during the first trimester, when organogenesis takes place, and harmful exposure may lead to structural abnormalities. It is well known that the use of drugs during pregnancy carries potential risk to both the mother and the foetus. General population and some health professionals appear to believe that prescription drugs are the major cause of birth defects. However, there is no data available supporting this theory (15). Usually between 2 and 4% of newborns have birth defects, and this number can increase during the months following delivery as some disorders become more evident. Only fewer than 1% of them are related to drug exposure (24).

1.2 Animal and human studies

During the process of development of a new drug, animal trials are very important and useful in order to check safety and establish a dose at which studies in humans may be undertaken.

Animal studies are fallible as a predictor of whether a drug or chemical is teratogenic in humans or not. The closer the experimental animal species is to humans, the greater the accuracy and precision of animal models in the prediction of human teratogenicity (1).

However, a further problem with animal teratology models is that the doses used are often a great deal higher than those taken by humans, even approaching maternally toxic doses. Such high doses and their toxic effects on the animal model can result in confusing interpretations of fetal outcome. There are also many differences in the way in which drugs and chemicals are absorbed by different species, for example placentation and embryonic development timing (1).

Mainly because of ethical and legal concerns, clinical trials in drug development commonly exclude pregnant women and as a consequence little is known about the effects on fetal and child development (18, 25-27). When a drug received its license for marketing there are still

unknown aspects. Usually drugs enter the market and are used by pregnant women without our being able to reliably predict whether they carry teratogenic risk or not for them or the foetus (15). Unfortunately, human teratogens are normally only discovered when a health professional sees a pattern emerge and can connect it to drug exposure during pregnancy. In this context, pharmacovigilance assumes a great importance. According to World Health Organization (WHO), pharmacovigilance (PV) is defined as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem"(28). When health care professionals detect any adverse effect of drugs they should report it to the responsible authorities. These reports can be useful in elaborating hypotheses which after subsequent study may lead to important conclusions. These actions may reduce the risk associated with the drug use by providing knowledge of which drugs should be used or avoided in specific circumstances such as pregnancy (29).

Despite all of this, animal trials have provided relevant information concerned with teratogenic effects of drugs; however as we said, animal models have limited predictive value for humans and as a consequence the findings may not reflect the true effects on them (30, 31).

Even with the fear of fetal malformation development when drugs are taken during pregnancy, recent international studies have demonstrated high prevalence of drugs being used among pregnant women (32, 33).

1.3 Drug use during pregnancy

1.3.1 Maternal Physiology during pregnancy and drug use

Pregnancy is a normal physiological state in which some changes take place; maternal enzymes, in particular cholinesterases, decrease their activity and maternal blood volume increases sharply in order to support the development of the foetus. Absorption of drugs follows similar kinetics as in nonpregnant women but renal clearance is increased and the enzyme activity is down-regulated (1).

Pregnant women, unsurprisingly, need medication, considering that they will probably have some disease or symptoms, whether related to the pregnancy (eg, vomiting or fever, constipation,

circulatory problems or urinary tract infection), or not. Therefore, physicians tend to use older drugs or herbal drugs because there is more experience with their use (34). Physicians are advised to prescribe the minimum number of drugs possible, to use the lowest effective doses (31) and always balance the risk/benefit before prescribing any medication (35-37). After a meticulous evaluation, the women should be fully informed of all the known and potential risks of the agent, as well as other therapeutic/ diagnostic options available (1, 14).

Exposure to OTC drugs is very common among pregnant women. They decide to take them without any medical advice because they think that if they can be sold without any prescription they must be safe. However, only a few OTC drugs have been proven to be safe for use during pregnancy, while others have unproven safety or are known to adversely affect the foetus. Limited information is available about the consequences of OTC drugs use (38).

The use of drugs may be unnecessary and even dangerous to the foetus, but in some situations like chronic therapies (e.g. epilepsy, diabetes mellitus, hypertension, etc.) and pregnancy related complications, drugs may be essential (33, 39, 40). In addition, there are potential benefits for the foetus as a healthy mother is essential for good fetal development (39).

1.3.2 Classification systems

Research on drug use may have some constraints because there are several drugs and those drugs may have different names and uses depending on the country. In order to analyse the use of drugs it is essential to adopt classification systems. Drug classification systems are used to provide a common language in order to be able to compare drug use data regionally, nationally or internationally, when the data has been codified in a uniform way. These systems can serve several purposes, such as identifying drug habits or problems of usage, and also educational interventions and monitoring the outcomes of such interventions.

The Anatomical Therapeutic Chemical Classification System (ATC) and the risk classification system of drugs from the US Food and Drug Administration (FDA), depending on the purpose, are the most common classification systems used in both American and European contexts (41-43).

ATC is one of the systems used to classify drugs and was developed and is frequently updated by the WHO. This system is composed of 5 levels, the final corresponding to the chemical substance. Drugs can also be coded using the ATC from the European Pharmaceutical Market Research Association (EphMRA) in which drugs are separated into groups at three or four different levels (44). The first system classifies substances according to the therapeutic or pharmaceutical aspects and in one category only (particular formulations or strengths can be given separate codes) and the second classifies products, mainly in accordance with their indications and use. As a consequence, it is possible to find the same compound in several classes, in either system. The objectives of these two classification systems are not the same: the WHO classification system is essentially used for international drug research while, the EphMRA was principally designed to satisfy the marketing needs for pharmaceutical companies, although it was originally based on the same ideas. It is used world-wide by International Medical Statistics (IMS) in order to create market research statistics for the pharmaceutical industry. Therefore, a direct comparison between these two systems is not easy. However, since 1991 there has been a conversation between the EphMRA classification committee and the WHO Collaborating Centre for Drug Statistics Methodology with the purpose of achieving better harmonization between the these two systems (45).

The ATC is a unique international reference system used in several countries. Active substances are divided into different groups according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties. There is a Centre and Working Group which aims to maintain stable codes so that tendencies in drug use may be studied over time without the complication of regular changes. When changes are requested for purposes not directly linked to drug consumption studies there is a great reluctance to make them (45).

It is also possible to classify drugs according to the American Society of Health-Systems Pharmacists (ASHP) (46). This system is based on pharmacological/therapeutic classification; drugs are allocated into a certain class number taking into account their action or use. This classification is most used in hospitals in the U.S., Canada and by some organizations or agencies amongst others.

There are some studies that choose to classify drugs according to active substance or therapeutic class and not any of the classification systems previously described (43).

In relation to risk classifications there are also many options. In 1978, the first classification system was implemented in Sweden and followed by the USA one year later. Both classification systems are based on clinical and animal data and give information on risks or safety of using drugs during pregnancy and lactation (47, 48).

The Swedish system (FASS) is composed of 4 categories: (A, B, C and D) and category B is divided into 3 other subgroups (B1, B2 and B3). Category A refers to safe drugs and B and D are used for drugs with possible different risks for the foetus depending on the evidence on which the risk is based (47).

In response to the thalidomide disaster, the FDA classification system was created and came into use in 1979, and like the previous system contains the categories A to D and in addition has another category called X for drugs confirmed to be teratogenic. The definitions used by the FDA and the FASS systems differ, which may lead to a different allocation of drugs. In 1989, the Australian Drug Evaluation Committee (ADEC) created a system using aspects of both classification systems using B1, B2 and B3 and X categories (47, 48).

The FASS classification system was adopted by the Netherlands, in 1987, and included category X in accordance with the Australian definition. A few years later, in 1991, Denmark developed its own classification system, which included 5 standardised phases whether a drug can be given or avoided during pregnancy. There is also a German classification with 11 categories; categories 1-3 include drugs that are expected to be safe, in categories 4 to 6 drugs were assumed to have been used only by a limited number of pregnant women, without an increased incidence of malformation or other severe adverse effects on the embryo, 7 is defined as direct or indirect effect on the foetus lasting temporarily or permanently, 8 “fetotoxic effect” is defined as direct or indirect effect on the foetus lasting temporarily or permanently, 9 includes medicinal products that may cause “perinatal complications or damages”, 10 exclusively includes effects caused by sexual hormones such as masculinizing effects on female foetus and 11 medicinal products causing an increased risk of mutagenic/cancerogenic effects (49).

Until now and despite all efforts, there is no uniform European risk classification system.

1.3.3 Prevalence of drug use

The prevalence of use according to studies carried out in different countries may differ, mainly because there are some studies that include supplements in the analysis and there are others that exclude them. The inclusion of vitamins and minerals will be reflected in the results by an increase in the estimated exposure.

Even with all the information available promoting the need to avoid the use of drugs during pregnancy, recent studies conducted among pregnant women show a high of prevalence of drug use during pregnancy, usually exceeding 70% when supplements are taken into account (31-33, 35, 41, 42, 50, 51). When the supplements are removed from the analysis the prevalences of use are usually higher than 40% (26, 33, 43).

A systematic review from Canada, which evaluated medicine use prescribed during pregnancy in developed countries showed that between 27 and 93% of pregnant women took at least one prescription drug excluding minerals and vitamins and between 57 and 99% including them. In this review only original English language studies were included along with those that evaluate populations residing in the 34 member countries of the Organization of the Economic Co-operative and Development (OECD). Studies that did not report the rates of prescription utilization and studies that only analysed a single period of pregnancy were excluded (52).

Despite all the classification systems, several studies were based on the FDA categories risk system and showed relatively low levels of use of potentially harmful drugs during pregnancy (category X), but differences may occur due to the study design or methodology (25, 31, 43).

1.3.4 Maternal determinants

In general and considering supplements, women who have a higher education level, greater income, claim to have had chronic diseases, attend more prenatal appointments, used the private health system, did not plan the pregnancy, declared complications during pregnancy, smoked and were primiparas are associated with a general increase of drug use during pregnancy (33, 50, 51, 53, 54).

According to a Brazilian study, mothers who attend more prenatal visits use more drugs in general and tend to avoid drugs with unknown fetal risk. Nevertheless, the drug usage is not associated with the beginning of prenatal assistance (33).

An Italian study showed that maternal drug usage is associated with historical medical problems and hospitalization during pregnancy. More frequent drug use was also connected with women over 30 years of age and also when the women had four or more ultrasound scans. This suggested that the more medical assistance the women had, the more they were likely to use drugs (50).

Data from an Irish study showed that women who used the public health service during pregnancy reported using drugs less frequently in relation to those who had private healthcare. Drug use was more commonly reported among women who did not plan the pregnancy or who had a multiple pregnancy. Women who declared that they had consumed alcoholic drinks before pregnancy took drugs more frequently than those who did not ever drink alcoholic beverages. In this study we also have the medical factors related to the use of FDA categories D and X (with the exception of oral contraceptives, fertility treatments and progestogens). Women who did not plan the pregnancy, who had multiple pregnancies, were smokers or were single were more likely to take drugs from these categories. Women who were unemployed had a higher likelihood of taking potentially dangerous drugs in comparison with women who had a profession. Women who organized antenatal care before 12 weeks of gestation were more likely to take drugs from categories D and X than women who only arranged antenatal care between 12 and 20 weeks of gestation (54)

A Canadian study established a relationship between maternal characteristics and exposure in pregnancy to FDA category C, D and X drugs. The most important determinant of exposure in pregnancy to these three categories was chronic diseases. Women aged less than 25 years old and who had higher parity (≥3) or who were receiving state benefits were more likely to be exposed to these categories of drugs, no matter what their chronic disease status was (55).

Women in Portugal usually use supplements (iron, magnesium, folic acid, vitamins, etc.) before and during pregnancy (56). In relation to the drugs used an insignificant number of descriptive studies have been undertaken and therefore very little information is available on this subject.

1.4 Objective of the study

To assess the prevalence of drug use before and during pregnancy and to estimate the maternal determinants of such use among mothers of the Generation XXI birth cohort.

2. Methods

Generation XXI is the first prospective Portuguese population-based birth cohort with participants recruited at delivery.

The overall aim of this cohort was to identify characteristics during pregnancy and infancy which influence development and health in later stages of life. Accompanying this cohort makes it possible to study the evolution of health parameters (such as social, behavioral, organizational, biological) in order to discover and understand the consequences of the prenatal phase of life as well as the first years of life on the health of individuals during adolescence and adulthood. This kind of study is fundamental in helping us gain a better understanding of public health.

2.1 Recruitment

The participants were recruited during the assembling of a birth cohort (Generation XXI), in Porto, North of Portugal. Recruitment was conducted in five public maternity units that cover six municipalities of the metropolitan area of Porto, Portugal (S. João Hospital, Santo António Hospital, Vila Nova de Gaia Hospital, Júlio Dinis Maternity and Pedro Hispano Hospital). All the maternities, except Júlio Dinis Maternity, are incorporated in a general hospital, with diverse medical and surgical specialties, and with differentiated perinatal support. These hospitals were responsible for 91.6% of the deliveries in the whole catchment population, with the remaining occurring in private hospitals/clinics.

From April 2005 to August 2006, pregnant women who gave birth at these five public maternities were invited to participate and 8% refused. The final sample was comprised of 8495 women who were delivered of live born infants (> 24 weeks) corresponding to 8647 newborns. Information on social and demographic characteristics, obstetric and gynecological history, lifestyles and current pregnancy events was obtained using a structured questionnaire. A sub-group of these women were invited during the first trimester and followed through the pregnancy because of specific objectives (n=313).

Interviews were performed 24 to 72 hours after delivery by trained interviewers. The study was approved by the Ethics Committee of the University of Porto Medical School/Hospital S. João

and written informed consent was obtained from each participant. Data were anonymously analysed both regarding the individuals and the hospitals where delivery took place.

Fig. 1: Eligible municipalities of Generation XXI birth cohort

2.2 Data collection

Through the interview, sociodemographic/socioeconomic characteristics such as age, education level, income, marital status, working condition were collected. Maternal age was categorized as less than 20 years, 20-29 years, 30-39 years, 40 years or more and education level was recorded as number of completed schooling years and categorized as ≤6 years, 7-9 years, 10-12 years and >12 years taking in account the Portuguese educational system. Marital status was divided into two categories (living with or without a partner), household monthly income was inquired in categories with 500€ intervals and categorized as ≤1000, 1001-1500, 1501-2000 and >2000. Working condition was defined as employed, unemployed, house-wife, students and retired (including women that were unable to work).

Medical history (health status before and during pregnancy), gynecological and obstetric history (number of pregnancies before the index pregnancy), lifestyles (smoking before pregnancy, alcohol and drug intake) and ante-natal care: health care provider system (public or private); age at the first prenatal care visit and number of visits (≤2, 3-6, 7-9 and ≥10) were collected during the interview. The participants' pre-pregnancy body mass index (BMI) was estimated from self-reported pre-pregnancy weight and height and was analysed according to the standard WHO

definition as underweight (<18.5kg/m^2), normal (18.5-24.9kg/m^2), overweight (25.0-29.9kg/m^2) and obese (≥30.0kg/m^2) (57). Women were asked if the current pregnancy was planned and if not, how they felt about it (planned, not planned but accepted and not planned and not accepted).

Information was also collected from the mothers regarding previous chronic pathologies (hypertension, thyroid disease, diabetes etc.) as well as pregnancy complications the mother had suffered from (gestational diabetes, hypertension, urinary tract infections etc.). The mother's social status at age 12 (high, intermediate or low) was also noted.

Drug use was also obtained using the questionnaire. Information was collected to assess drug use at two different times: three months before and during pregnancy.

Two questions were asked for the period before pregnancy; the first one was related to supplements and the second one to other drugs that women used. The first question was: "In the last three months before getting pregnant did you take any vitamin, mineral or folic acid supplement?". If yes, the women were asked about the commercial name of each supplement, the daily dose, who recommended it (physician, pharmacist or other) and the duration of the treatment. The women were also asked if they had stopped taking the supplement before or after being pregnant and when. The second question was: "In the three months before getting pregnant did you take any other medicine (chronic therapy, contraceptives, sleeping pills, antibiotics, antidepressants, natural products, etc.)?". If yes, the women were asked the commercial name of the drug and the dosage, the clinical reason for using it, the daily dose and if she had stopped or not before or after getting pregnant and when.

Drugs used during pregnancy were obtained using the question "During pregnancy did you take any drug (chronic therapy, folic acid, analgesics, antibiotics, sleeping pills, natural products, etc.)". Drug users also provided the following information: commercial name and dosage of each medicine, reason for using it, daily dose, gestational age (weeks and days) at the beginning and end of use and who recommend it (physician, pharmacist or other).

Based on this data we were able to estimate the drug use by trimester: drugs used in the first 12 weeks of pregnancy were considered as having been taken in the first trimester; in weeks 13 to 28 as having been used in the second trimester and after week 28 having been used in third trimester.

2.3 Drug classification

All the drugs that the women took before and during pregnancy were coded using the WHO ATC codification system (45), 2013, up to the maximum possible level.

The ATC classification system codes drugs according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties, into 14 main groups and it is composed of seven alpha-numeric characters. Drugs are classified in groups at five different levels (**Figure 2**).

Fig. 2: Anatomical Therapeutic Chemical Classification (ATC) structure

The first one (one digit) refers to the anatomical main group, the second (two digits) to the therapeutic subgroup, the third (one digit) to the pharmacological subgroup, the fourth (one digit) to the chemical subgroup and the last one to the chemical substance (two digits).

The 14 main ATC categories are defined as : A- Alimentary tract and Metabolism; B- Blood and blood forming organs; C-Cardiovascular system; D- Dermatologicals; G- Genito urinary system and sex hormones; H- Systemic hormonal preparations, excl. sex hormones and insulins; J- Antiinfectives for systemic use; L- Antineoplastic and immunodulating agents; M- Musculo-skeletal system; N-Nervous system; P-Antiparasitic products, insecticides and repellents; R-Respiratory system; S-Sensory organs and V-Various (45). A detailed description of the classification up to the second level is available in annex 1.

Some drugs may have different ATC codes if the active substance is available in two or more formulations with clearly different therapeutic uses (45).

Drugs were coded according to the main active substance. If more than one code was available, we decided to analyse the reason for use and the dose and based on this, to classify the drug.

In some situations we were unable to classify the drugs according to the ATC code; in cases where the drug name reported by the mother was unidentifiable (244 drugs) and when the women did not know the drug name (20 drugs). There were also cases where insufficient information was given (530 drugs), for example the woman knew the indication but did not

know the complete name of the drug or in some cases it was necessary to know the dose in order to classify the drug. In all of these situations a great deal of effort was put into trying to discover what the drug was before classifying it as unknown. To do that, the clinical reason for taking the drug, the dosage and the frequency of use were considered. Obstetric counseling on the main prescribed and used drugs during pregnancy was also obtained.

Drugs were also classified according their fetal risk, using the FDA risk classification system.

We used Autoridade Nacional do Medicamento e Produtos de Saúde IP (Infarmed) publications (Prontuário Terapêutico [PT]) to check the risk category (based on FDA risk classification system) (58). We decided to use publications from December 2004 (PT 5) and August 2011 (PT 10) because some drugs may have changed their risk category. The first publication was the most recent one available in the year that data on drug use was collected and the second one is the latest publication that we had access to considering that our drug classification started at the end of the year 2012.

The pregnancy categories used were: Category A- no fetal risk, safe for use in pregnant women; Category B- absence of fetal risk, demonstrated by animal experiments or in human studies; Category C- unknown fetal risk, due to the lack of extended studies; Category D-fetal evidence in animals, but the necessity can justify the risk and Category X- harmful to the foetus, the risk exceeds the benefit, and so this is not recommended in pregnancy. As we were coding the drugs, we decided to create a new category that we called E: when we could not kwon the risk category because the classification was available only for specific trimesters. Drugs that the risk could not be classified into one of the previous categories were categorized as “unknown risk”.

2.4 Data analysis

From 8495 participants we decided to exclude 313 women who belong to the sub-cohort since pre-pregnancy characteristics were self-reported in the first trimester and their report was likely to change over time during pregnancy. We also excluded the women who did not know if they had taken any drugs (137 women). Therefore, 8045 women were included in our study. When analysing the prevalence of drug use by ATC categories and FDA fetal risk categories, 159 women were also excluded because they had taken drugs but they did not know their names (final sample of 7886 women).

The total number of drugs and the proportion of drugs recommended by a physician were calculated. The prevalence (and respective 95% confidence interval [CI]) of drug use before pregnancy, during pregnancy and for both of these moments was estimated. Prevalence estimates were computed including and excluding the most used vitamin and mineral supplements: ATC codes A11, A12 and B03. Prevalence estimates were also computed according to the ATC (up to the second level) and the FDA classification systems separately for each trimester (1^{st}, 2^{nd}, and 3^{rd}).

Among drug users, and for each time period, the mean number of medicines per woman and the respective standard deviation (SD) was calculated.

The duration of use of each category of ATC drugs was estimated subtracting the gestational age at the beginning of use from the gestational age at the end of use. If the woman used more than one drug from each category we assumed the lowest duration of utilization. The median, minimum, maximum and respective 25^{th} and 75^{th} percentiles or interquartile range (IQR) are presented for all first level ATC categories and for six second level subgroups (A04, G03, J01, N02, N05 and N06) because of their higher prevalence or potential fetal risk.

Maternal characteristics were compared according to the use of drugs before and during pregnancy using chi-square tests. Odds ratio (OR) and respective 95% confidence intervals (CI) were obtained fitting univariate and multivariate logistic regression models estimating the association between each maternal characteristic and the drug use at each moment. All the significant maternal characteristics ($p<0.10$) in the univariate analysis were included, one by one, in the multivativate models. All the variables that remained significant were maintained.

Statistical analysis was performed using SPSS software package (SPSS 20.0 for Windows, SPSS Inc., Chicago, IL, USA).

Out of a total of 8045 women, the mean age was 28.96 (SD=5.573). Most women lived with a partner (93.9%) and the average educational level was 10.50 years (SD=4.262). About 35% had a monthly family income below 1000€, the majority of the pregnancies were planned (67.0%) and it was the first delivery for more than half of the women in the study (55.9%).

3. Results

3.1 Overall use

The prevalence of overall drug use before conception and during pregnancy was respectively 49.2% (95% IC: 48.2-50.3) and 98.3% (95% IC: 98.0-98.6). In both time periods 30.8% (95% IC: 29.8-31.8) of women took drugs. When the supplements were excluded, the estimated prevalence of drug use before, during pregnancy and in both time periods decreased to 34.9% (95% IC: 33.9-35.9), 60.2% (95% IC: 59.2-61.3) and 15.3% (95% IC: 14.5-16.1), respectively.

Before pregnancy, 5537 drugs were reported, corresponding to 1.35 drugs per woman. During pregnancy the number of drugs increased to 27775, corresponding to 3.51 drugs per woman.

For 4124 drugs used before pregnancy (74.5%) women did not provide information about who recommended them, 1393 were prescribed by physicians, 4 indicated by pharmacists and 16 by another person. Excluding the drugs without any information, 98.6% were reported to have been prescribed by physicians. In relation to the consumption of drugs during pregnancy and regarding the 27775 drugs, for 3917 of them (14.1%) no data was available about the person who indicated them, 23744 were prescribed by doctors, 23 indicated by pharmacists and 91 by another person. Removing the drugs without information, 99.5% were reported to have been prescribed by physicians.

3.2 Drug use according ATC classification

In **Table 1** the prevalence of drug use according to the main ATC categories before and during pregnancy is shown.

Table 1: Prevalence of drug use before and during pregnancy according to the ATC classification system

Drug category		n=7886	
		Before Pregnancy n (%)	**During Pregnancy** n (%)
A	*Alimentary tract and Metabolism*	237 (3.0)	5238 (66.4)
A02	Drugs for acid related disorders	32 (0.3)	678 (8.6)
A04	Antiemetics and antinauseants	1 (0.0)	1241 (15.7)
A11	Vitamins	111 (1.4)	1614 (20.5)
A12	Mineral Supplements	44 (0.6)	3418 (43.3)
B	*Blood and blood forming organs*	1509 (19.1)	7521 (95.4)
B01	Antithrombotic agents	22 (0.3)	359 (4.6)
B03	Antianemic preparations	1494 (18.9)	7513 (95.3)
C	*Cardiovascular system*	116 (1.5)	636 (8.1)
C02	Antihypertensives	5 (0.1)	69 (0.9)
C05	Vasoprotectives	31 (0.4)	474 (6.0)
C07	Beta blocking agents	26 (0.3)	27 (0.3)
C08	Calcium channel blockers	9 (0.1)	54 (0.7)
D	*Dermatologicals*	7 (0.1)	20 (0.3)
G	*Genito urinary system and sex hormones*	1797 (22.8)	926 (11.7)
G01	Gynecological antiinfectives and antiseptics	9 (0.1)	343 (4.3)
G03	Sex hormones and modulators of the genital system	1772 (22.5)	594 (7.5)
H	*Systemic hormonal preparations. excl. sex hormones and insulins*	100 (1.3)	116 (1.5)
J	*Antiinfectives for systemic use*	241 (3.1)	1292 (16.4)
J01	Antibacterials for systemic use	226 (2.9)	1271 (16.1)
L	*Antineoplastic and immunodulating agents*	11 (0.1)	7 (0.1)
M	*Musculo-skeletal system*	108 (1.4)	77 (1.0)
N	*Nervous system*	577 (7.3)	1551 (19.7)
N02	Analgesics	238 (3.0)	1202 (15.2)

Drug category		n=7886	
		Before Pregnancy n (%)	**During Pregnancy** n (%)
N05	Psycholeptics	236 (3.0)	351 (4.5)
N06	Psychoanaleptics	144 (1.8)	103 (1.3)
P	Antiparasitic products. insecticides and repellents	6 (0.1)	6 (0.1)
R	Respiratory system	98 (1.2)	194 (2.5)
S	Sensory organs	3 (0.0)	6 (0.1)
V	Various	22 (0.3)	36 (0.5)
	Unknown drug name	184 (2.3)	445 (5.6)

Table 1: *continued*

The most common preconception drugs were those from genito urinary system and sex hormones (G) and blood and blood forming organs (B) and were taken respectively by 22.8% and 19.1% of women. Almost all drugs from category B were referent to the use of antianemic preparations (B03) and those from category G were essentially sex hormones and modulators of the genital system (G03).

During pregnancy, 95.4% of women reported having used drugs from the blood and blood forming organs category (B), 66.4% from the alimentary tract and metabolism category (A), 19.7% from the nervous system category (N) and 16.4% from the antiinfectives for systemic use category (J). Category A had a greater increase in the prevalence of use essentially because of utilization of vitamins (A11, 20.5%) and minerals (A12, 43.3%) and category B due to the use of antianemic preparations (B03, 95.3%). The use of drugs from category J rose from 3.1% before to 16.4% during pregnancy mainly because of the increase in the use of antibacterials for systemic use (J01, 16.1%). Drugs for the nervous system (N) changed from 7.3% before pregnancy to 19.7% in pregnancy. Almost all nervous system drugs were analgesics and anti-pyretics (N02), especially acetaminophen (N02BE01), used by 15.2% of the women during pregnancy. The prevalence of use of psycholeptics drugs (N05) increased from 3.0% to 4.5% during pregnancy. Among these drugs, the most frequently reported was valerian (N05CM09).

In **Table 2** the prevalence estimates of drug use in each trimester of pregnancy are presented.

Table 2: Drugs used during pregnancy (1st, 2nd and 3rd trimesters) according to ATC classification system

Drug category	During Pregnancy (n=7886)			
	1st Trimester	2nd Trimester	3rd Trimester	Unknown
	n (%)	n (%)	n (%)	n (%)
A	1985 (25.2)	3078 (39.0)	3431 (43.5)	1801 (22.8)
A04	762 (9.7)	605 (7.7)	282 (3.6)	407 (5.2)
A11	783 (9.9)	1055 (13.4)	936 (11.9)	433 (5.5)
A12	579 (7.3)	1763 (22.4)	2420(30.7)	1051 (13.3)
B	4902 (62.2)	5439 (69.0)	5492 (69.6)	2366 (30.0)
C	150 (1.9)	294 (3.7)	429 (5.4)	195 (2.5)
D	6 (0.1)	3 (0.0)	8 (0.1)	7 (0.1)
G	481 (6.1)	174 (2.2)	139 (1.8)	301 (3.8)
G03	425 (5.4)	85 (1.1)	10 (0.1)	174 (2.2)
H	53 (0.7)	47 (0.6)	51 (0.6)	65 (0.8)
J	247 (3.1)	419 (5.3)	402 (5.1)	491 (6.2)
J01	236 (3.0)	409 (5.2)	390 (5.0)	480 (6.1)
L	5 (0.1)	2 (0.0)	2 (0.0)	3 (0.0)
M	31 (0.4)	13 (0,2)	10 (0.1)	27 (0.3)
N	396 (5.0)	351 (4.5)	357 (4.5)	979 (12.4)
N02	197 (2.5)	238 (3.0)	230 (2.9)	819 (10.4)
N05	153 (1.9)	96 (1.2)	117 (1.5)	138 (1.7)
N06	81 (1.0)	16 (0.2)	10 (0.1)	27 (0.3)
P	1 (0.0)	1 (0.0)	3 (0.0)	2 (0.0)
R	59 (0.7)	57 (0.7)	57 (0.7)	99 (1.3)
S	1 (0.0)	1 (0.0)	1 (0.0)	3 (0.0)
V	25 (0.3)	15 (0.2)	13 (0.2)	10 (0.1)

For most drug categories the prevalence of drug use remained relatively constant during the trimesters of pregnancy. The use of drugs from the alimentary tract and metabolism category (A), the blood and blood forming organs category (B) and the cardiovascular system category (C) increased from the first to the third trimester. This increase was more evident in the first

category mentioned (25.2%, 39.0% and 43.5% respectively, in 1st, 2nd and 3rd trimesters), essentially due to the increase in the use of mineral supplements (A12). At the same time the use of antiemetic (A04) drugs decreased.

Drugs from the genito urinary system and sex hormones category (G) decreased throughout pregnancy, due primarily to a decrease in the use of sex hormones and modulators of the genital system (G03) drugs.

The median duration of drugs used by women during pregnancy (in days) is represented in **Table 3** for the main 14 ATC categories and for the 2nd level ATC subgroups.

Table 3: Characterization of the duration of drug use for the main ATC categories using descriptive measures

Drug category	n	Minimum (days)	Median (days) (p25-p75)	Maximum (days)
A	3859	0	105 (49-175)	280
A04	851	0	77 (42-175)	273
B	5924	0	168 (119-196)	287
C	476	0	84 (35-161)	287
D	13	1	42 (10-112)	273
G	653	0	28 (7-63)	273
G03	429	7	56 (28-84)	273
H	68	1	143 (42-266)	280
J	841	0	7 (6-7)	287
J01	826	0	7 (6-7)	287
L	5	42	84 (45-245)	280
M	51	0	21 (7-42)	147
N	660	0	28 (7-147)	294
N02	398	0	14 (3-196)	294
N05	230	0	42 (26-105)	280
N06	82	7	56 (28-70)	280
P	4	0	*	84

Drug category	n	Minimum (days)	Median (days) (p25-p75)	Maximum (days)
R	113	0	21 (7-70)	280
S	3	3	*	21
V	27	14	112 (49-217)	266

Table 3: *continued*

*Insufficient data for calculating these descriptive measures

Drugs from the blood and blood forming organs category (B) and from category H (systemic hormonal preparations excluding sex hormones and insulins) showed a higher median duration of utilization: 168 and 143 days, respectively, although more variability in the duration of use of drugs can be seen in category H (IQR=224). Antiinfectives for systemic use category (J) had a median of 7 days with a low variability (IQR=1).

3.3 Drug use according FDA risk assessment

Drugs that women used during pregnancy were classified according to the fetal risk category from Infarmed Publications and are represented in **Table 4**.

Table 4: Drugs used during pregnancy according to the fetal risk category (Infarmed Publications 2004 and 2011)

Risk category		n=7886 During Pregnancy	
		PT 5 (2004) n (%)	PT 10 (2011) n (%)
A	No fetal risk, safe for use in pregnant women	7223 (91.6)	7223 (91.6)
B	Absence of fetal risk, demonstrated by animal experiments or in human studies	2417 (30.6)	2287 (29.0)
C	Unknown fetal risk, due to the lack of extended studies	720 (9.1)	1569 (18.9)
D	Fetal evidence in animals, but the necessity can justify the risk	536 (6.8)	685 (8.7)
X	Harmful to the foetus, the risk exceeds the benefit, and so this is contraindicated in pregnancy	15 (0.2)	19 (0.2)

Risk category		n=7886 During Pregnancy PT 5 (2004) n (%)	PT 10 (2011) n (%)
Categories created for the current study:			
E	Known the risk category only if used in specific trimesters, but if the trimester changed we would not know the exact risk;	195 (2.5)	233 (3.0)
Unknown	Unknown risk category	5944 (75.4)	5722 (91.6)

Table 4: *continued*

PT- Prontuário Terapêutico (Infarmed Publication).

During pregnancy and according to the 2011 Infarmed publication, drugs from category A and category B were used by 91.6% and 29.0% of women respectively. Category C was used by 18.9% of the women and category D and X were taken by 8.7% and 0.2% of women respectively. When we used the 2004 Infarmed publication to classify the drugs, the percentage of use for category C and D decreased to 9.1% and 6.8% respectively. Category X remained the same in both publications.

During pregnancy, and independently of which publication we used, the percentage of women who used drugs from category E remained similar (2.5% vs. 3.0%).

In **table 5** drug use during pregnancy and according to trimester is summarised, using the 2011 Infarmed Publication.

Table 5: Drugs used during pregnancy (1st, 2nd and 3rd trimesters) according to the fetal risk category (Infarmed Publication 2011);

Risk category	During Pregnancy 1st Trimester N (%)	2st Trimester N (%)	3rd Trimester N (%)	Unknown N (%)
A	4750 (60.0)	5046 (64.0)	4900 (62.1)	731 (9.3)
B	451 (5.7)	754 (9.6)	840 (10.7)	889 (11.3)
C	711 (9.0)	293 (6.3)	529 (6.7)	177 (2.2)

	During Pregnancy			
Risk category	**1st Trimester** N (%)	**2st Trimester** N (%)	**3rd Trimester** N (%)	**Unknown** N (%)
D	364 (4.6)	338 (4.3)	364 (4.6)	69 (0.9)
X	13 (0.2)	2 (0.0)	1 (0.0)	3 (0.0)
E	80 (1.0)	65 (0.8)	81 (1.0)	15 (0.2)
Unknown risk category	2229 (28.3)	3353 (42.5)	3745 (47.5)	1184 (15.0)

Table 5: *continued*

The proportion of women who used drugs from category B increased from 5.7% to 10.7% as the pregnancy progressed while those from category C decreased from 9.0% to 6.7%. Category A underwent a small increase of use during the second trimester. The use of drugs from categories D and X was similar in all trimesters.

In **Table 6** the association between maternal socio-demographic and health characteristics and drug use before pregnancy is presented.

Table 6: Relation between the use of drugs **before pregnancy** and socio-demographic/ health maternal characteristics including and excluding supplements

	All drugs			Excluding Supplements [a]		
	n (%)	Crude Model OR (95% CI)	Adjusted Model [b] OR (95% CI)	n (%)	Crude Model OR (95% CI)	Adjusted Model [b] OR (95% CI)
Maternal Age						
<20	113 (42.5)	0.73 (0.57-0.95)	0.80 (0.62-1.04)	104 (39.1)	1.06 (0.82-1.38)	1.08 (0.83-1.40)
20-29	1658 (50.2)	1.00	1.00	1244 (37.6)	1.00	1.00
30-39	1644 (50.4)	1.01 (0.92-1.12)	0.99 (0.89-1.11)	1030 (31.6)	0.77 (0.69-0.85)	0.77 (0.69-0.86)
≥40	79 (44.6)	0.80 (0.59-1.09)	0.88 (0.64-1.20)	62 (35.0)	0.89 (0.65-1.23)	0.87 (0.63-1.20)
	p=0.040			***p<0.001***		
Education level						
≤6	668 (43.4)	0.57 (0.49-0.65)	0.69 (0.58-0.82)	566 (36.8)	1.31 (1.13-1.51)	1.09 (0.91-1.31)
7-9	830 (47.5)	0.67 (0.59-0.76)	0.76 (0.65-0.90)	651 (37.2)	1.33 (1.16-1.53)	1.08 (0.91-1.28)
10-12	969 (50.1)	0.74 (0.65-0.85)	0.78 (0.68-0.90)	673 (34.8)	1.20 (1.05-1.38)	1.02 (0.87-1.18)
>12	1027 (57.5)	1.00	1.00	550 (30.8)	1.00	1.00
	p<0.001			***p<0.001***		
Living with a partner						
Yes	3332 (50.0)	1.13 (0.91-1.41)	1.05 (0.84-1.32)	2291 (34.4)	0.69 (0.55-0.86)	0.76 (0.60-0.95)
No	158 (46.9)	1.00	1.00	146 (43.3)	1.00	1.00
	p=0.289			***p=0.001***		
Monthly Income (€)						
≤1000	1280 (45.8)	1.00	1.00	1054 (37.8)	1.00	1.00
1001-1500	976 (50.3)	1.20 (1.07-1.34)	1.09 (0.96-1.23)	689 (35.5)	0.91 (0.81-1.02)	0.94 (0.83-1.07)
1501-2000	585 (54.0)	1.39 (1.20-1.59)	1.17 (1.00-1.37)	359 (33.1)	0.82 (0.70-0.95)	0.89 (0.76-1.06)
>2000	599 (55.0)	1.44 (1.25-1.66)	1.13 (0.95-1.35)	308 (28.3)	0.65 (0.56-0.76)	0.73 (0.61-0.88)
Prefer not to say	54 (52.9)	1.33 (0.89-1.97)	1.21 (0.81-1.81)	30 (29.4)	0.69 (0.45-1.06)	0.73 (0.47-1.12)
	p<0.001			***p<0.001***		
Working Condition						
Employed	2672 (51.7)	1.00	1.00	1755 (34.0)	1.00	1.00
Student/Retired	59 (47.2)	0.83 (0.59-1.19)	0.91 (0.62-1.34)	50 (40.0)	1.30 (0.90-1.86)	1.12 (0.76-1.65)
Housewife	152 (40.4)	0.63 (0.51-0.78)	0.81 (0.65-1.02)	130 (34.6)	1.03 (0.82-1.28)	0.90 (0.61-1.13)
Unemployed	608 (45.7)	0.79 (0.70-0.89)	0.88 (0.77-1.00)	503 (37.8)	1.18 (1.04-1.34)	1.02 (0.89-1.17)
	p<0.001			***p=0.040***		

Table 6: *Continued*

	All drugs			Excluding Supplements [a]		
	n (%)	Crude Model OR (95% CI)	Adjusted Model [b] OR (95% CI)	n (%)	Crude Model OR (95% CI)	Adjusted Model [b] OR (95% CI)
Social Status at 12 years old						
High	929 (55.2)	1.00	1.00	542 (32.2)	1.00	1.00
Intermediate	1706 (49.3)	0.79 (0.70-0.89)	0.91 (0.80-1.03)	1242 (35.9)	1.18 (1.04-1.33)	1.05 (0.92-1.21)
Low	761 (45.6)	0.68 (0.59-0.78)	0.88 (0.75-1.04)	598 (35.8)	1.17 (1.02-1.35)	1.05 (0.89-1.25)
	p<0.001			***p=0.026***		
Parity						
Primipara	2088 (53.1)	1.00	1.00	1362 (34.6)	1.00	1.00
Multipara	1406 (45.7)	0.74 (0.68-0.82)	0.79 (0.71-0.98)	1078 (35.1)	1.02 (0.92-1.13)	1.10 (0.98-1.23)
	p<0.001			*p=0.729*		
Planned Pregnancy						
Yes	2474 (51.2)	1.00	1.00	1452 (30.1)	1.00	1.00
No but accepted	958 (46.6)	0.83 (0.75-0.92)	0.93 (0.83-1.04)	926 (45.0)	1.90 (1.71-2.12)	1.88 (1.68-2.11)
No and not accepted	61 (53.5)	1.10 (0.76-1.59)	1.34 (0.91-1.96)	61 (53.5)	2.68 (1.84-3.89)	2.47 (1.69-3.62)
	p=0.001			***p<0.001***		
Chronic disease						
Yes	2272 (54.3)	1.56 (1.42-1.72)	1.52 (1.38-1.68)	1603 (38.3)	1.48 (1.33-1.64)	1.53 (1.38-1.69)
No	1222 (43.2)	1.00	1.00	837 (29.6)	1.00	1.00
	p<0.001			***p<0.001***		
BMI (kg/m2) before pregnancy						
<18.5	123 (49.4)	0.89 (0.69-1.15)	0.90 (0.69-1.17)	96 (38.6)	1.14 (0.88-1.49)	1.11 (0.85-1.45)
18.5-24.9	2225 (52.2)	1.00	1.00	1511 (35.5)	1.00	1.00
25.0-29.9	680 (49.0)	0.88 (0.78-0.99)	0.93 (0.82-1.06)	498 (35.9)	1.02 (0.90-1.16)	0.98 (0.87-1.12)
≥30.0	279 (47.4)	0.82 (0.69-0.98)	0.91 (0.76-1.08)	207 (35.1)	0.99 (0.82-1.18)	0.92 (0.76-1.10)
	p=0.043			*p=0.783*		
Smoke before pregnancy						
Yes	851 (47.1)	0.86 (0.77-0.96)	0.90 (0.81-1.01)	679 (37.6)	1.18 (1.05-1.32)	1.14 (1.02-1.28)
No	2617 (50.8)	1.00	1.00	1742 (33.8)	1.00	1.00
	p=0.007			***p=0.004***		

a – Excluding drugs from ATC code A11, ATC code A12 and ATC code B03;
b – Adjusted for maternal age, education level, chronic disease, parity and monthly income.

The prevalence of drug use before pregnancy was higher among women aged 20-39 (50.3%), with more than 12 years of education (57.5% vs. <12years: 47.2%) and with a higher income (>2000:55.0% vs. <2000:48.8%). The prevalence was also more frequent among employed women (51.7% vs. 44.7%) and in those that had a higher childhood social status (55.2% vs. 48.1%). Primiparous women (53.1% vs. 45.7) and those that had not accepted the current pregnancy (53.5% vs.49.8%) were also more likely to use drugs before pregnancy. The same was observed among women who had chronic diseases (54.3% vs. 43.2%), had a lower pre-pregnancy BMI (<25.0: 52.1% vs. ≥25.0: 48.5%) and who were non-smokers (58.8% vs. 47.1%).

Excluding the use of supplements, only the existence of chronic diseases and not planning the current pregnancy remained associated in the same way as stated above. Most of the other characteristics remained associated with the drug use but in different directions. The use of drugs was more frequent among the youngest women, with less education, those who lived without a partner, had a lower income, were students/retired, belonged to an intermediate social status and had smoked before pregnancy.

After adjusting the models, only education, parity and chronic diseases remained associated with drug use. The use of drugs decreased significantly at the same time as the educational level decreased (vs. >12 years: 10-12: OR=0.78; 95%CI: 0.68-0.90, 7-9: OR=0.76; 95%CI: 0.65-0.90 and ≤6: OR=0.69; 95%CI: 0.58-0.82). Primiparous women (multipara: OR=0.79; 95%CI: 0.71-0.98) and women who reported to have some chronic diseases (OR=1.52; 95%CI: 1.38-1.68) were more likely to have used drugs before pregnancy.

After excluding supplements from the analysis, the educational level and parity were no longer significantly associated with the use of drugs before pregnancy. However, having reported chronic diseases remained associated with the use of drugs (OR=1.53; 95%CI: 1.38-1.69). Living with a partner (OR=0.76; 95%CI: 0.60-0.95), had not planned the current pregnancy (vs. planned: not planned but accepted: OR=1.88; 95%CI: 1.68-2.11, not planned and not accepted: OR=2.47; 95%CI: 1.69-3.62) and had smoked before pregnancy (OR=1.14; 95%CI: 1.02-1.28), are characteristics that became associated with drug use.

In **Table 7** the association between maternal socio-demographic and health characteristics and drug use during pregnancy is presented.

Table 7: Relation between the use of drugs **during pregnancy** and socio-demographic/ health maternal characteristics including and excluding supplements

	All drugs			Excluding Supplements [a]		
	n (%)	Crude Model OR (95% CI)	Adjusted Model [b] OR (95% CI)	n (%)	Crude Model OR (95% CI)	Adjusted Model [b] OR (95% CI)
Maternal Age						
<20	396 (96.4)	0.44 (0.25-0.78)	1.21 (0.62-2.33)	249 (60.6)	1.04 (0.84-1.28)	1.09 (0.88-1.35)
20-29	3590 (98.4)	1.00	1.00	2179 (59.7)	1.00	1.00
30-39	3500 (98.7)	1.30 (0.88-1.92)	1.01 (0.79-1.85)	2155 (60.8)	1.05 (0.95-1.15)	1.00 (0.91-1.11)
≥40	193 (96.0)	0.40 (0.19-0.86)	0.52 (0.23-1.18)	124 (61.7)	1.09 (0.81-1.46)	1.06 (0.79-1.43)
	p<0.001			*p=0.781*		
Education level						
≤6	1736 (96.1)	0.21 (0.12-0.36)	0.49 (0.26-0.93)	1053 (58.3)	0.82 (0.72-0.93)	0.84 (0.72-0.97)
7-9	1970 (98.5)	0.54 (0.29-0.99)	1.18 (0.60-2.34)	1188 (59.4)	0.85 (0.75-0.97)	0.86 (0.75-0.99)
10-12	2089 (99.5)	1.77 (0.80-3.92)	2.58 (1.14-5.82)	1267 (60.4)	0.89 (0.78-1.01)	0.90 (0.78-1.02)
>12	1885 (99.2)	1.00	1.00	1200 (63.1)	1.00	1.00
	p<0.001			***p=0.017***		
Living with a partner						
Yes	7214 (98.4)	1.78 (1.00-3.19)	1.03 (0.54-1.98)	4400 (60.0)	0.83 (0.68-1.01)	0.83 (0.68-1.01)
No	457 (97.2)	1.00	1.00	303 (64.5)	1.00	1.00
	p=0.073			*p=0.064*		
Monthly Income (€)						
≤1000	2694 (97.9)	1.00	1.00	1639 (59.6)	1.00	1.00
1001-1500	1893 (98.7)	1.70 (1.05-2.74)	0.81 (0.48-1.37)	1152 (60.1)	1.02 (0.91-1.15)	0.97 (0.85-1.10)
1501-2000	1067 (99.2)	2.55 (1.26-5.17)	1.05 (0.48-2.32)	640 (59.5)	1.00 (0.86-1.15)	0.89 (0.76-1.05)
>2000	1065 (99.2)	2.55 (1.26-5.16)	0.94 (0.39-2.24)	679 (63.2)	1.17 (1.01-1.35)	0.98 (0.82-1.17)
Prefer not to say	103 (98.1)	1.11 (0.27-4.60)	0.82 (0.18-3.85)	70 (66.7)	1.36 (0.90-2.05)	1.29 (0.85-1.97)
	p=0.006			*p=0.160*		
Working Condition						
Employed	5537 (99.1)	1.00	1.00	3372 (60.3)	1.00	1.00
Student/Retired	212 (98.6)	0.66 (0.21-2.14)	1.96 (0.54-7.11)	133 (61.9)	0.66 (0.21-2.14)	1.15 (0.86-1.53)
Housewife	418 (92.5)	0.12 (0.07-0.18)	0.27 (0.16-0.46)	247 (54.6)	0.12 (0.07-0.18)	0.90 (0.74-1.11)
Unemployed	1495 (97.5)	0.37 (0.24-0.56)	0.54 (0.34-0.86)	945 (61.6)	0.37 (0.24-0.56)	1.10 (0.98-1.25)
	p<0.001			*p=0.060*		

Table 7: *Continued*

	Including Supplements			Excluding Supplements [a]		
	n (%)	Crude Model OR (95% CI)	Adjusted Model [b] OR (95% CI)	n (%)	Crude Model OR (95% CI)	Adjusted Model [b] OR (95% CI)
Social Status at 12 years old						
High	1819 (99.2)	1.00	1.00	1135 (61.9)	1.00	1.00
Intermediate	3776 (98.4)	0.52 (0.29-0.92)	0.90 (0.47-1.73)	2296 (59.9)	0.92 (0.82-1.03)	1.02 (0.90-1.15)
Low	1857 (97.4)	0.31 (0.18-0.56)	0.91 (0.45-1.86)	1141 (59.9)	0.92 (0.81-1.05)	1.07 (0.91-1.25)
	p<0.001			*p=0.302*		
Parity						
Primipara	4324 (98.9)	1.00	1.00	2662 (60.9)	1.00	1.00
Multipara	3263 (97.7)	0.47 (0.33-0.68)	0.88 (0.59-1.31)	1982 (59.3)	0.94 (0.86-1.03)	0.98 (0.89-1.08)
	p<0.001			*p=0.177*		
Planned Pregnancy						
Yes	5196 (98.6)	1.00	1.00	3073 (58.5)	1.00	1.00
No but accepted	2339 (97.3)	0.38 (0.27-0.55)	0.73 (0.49-1.09)	1527 (63.5)	1.23 (1.12-1.36)	1.31 (1.18-1.46)
No and not accepted	140 (96.6)	0.30 (0.12-0.77)	1.16 (0.39-3.42)	106 (73.1)	1.93 (1.33-2.79)	2.09 (1.43-3.06)
	p<0.001			***p<0.001***		
Chronic disease						
Yes	4523 (98.6)	1.35 (0.95-1.91)	0.95 (0.65-1.39)	2986 (65.1)	1.62 (1.48-1.78)	1.53 (1.39-1.68)
No	3150 (98.1)	1.00	1.00	1717 (53.5)	1.00	1.00
	p=0.111			***p<0.001***		
BMI (kg/m2) before pregnancy						
<18.5	299 (98.7)	0.91 (0.33-2.53)	0.98 (0.34-2.82)	201 (66.3)	1.29 (1.01-1.65)	1.28 (1.00-1.64)
18.5-24.9	4676 (98.8)	1.00	1.00	2861 (60.4)	1.00	1.00
25.0-29.9	1499 (97.5)	0.48 (0.32-0.73)	0.52 (0.33-0.81)	951 (61.9)	1.06 (0.94-1.20)	1.07 (0.94-1.20)
≥30.0	625 (98.1)	0.64 (0.34-1.19)	0.69 (0.36-1.35)	401 (63.0)	1.11 (0.94-1.32)	1.11 (0.93-1.33)
	p=0.005			*p=0.132*		
Smoke before pregnancy						
Yes	1982 (97.6)	1.78 (1.24-2.56)	0.64 (0.44-0.95)	1295 (63.8)	1.22 (1.10-1.35)	1.27 (1.14-1.41)
No	5698 (98.6)	1.00	1.00	3413 (59.1)	1.00	1.00
	p=0.002			***p<0.001***		

Table 7: Continued

	Including Supplements			Excluding Supplements [a]		
	n (%)	Crude Model OR (95% CI)	Adjusted Model [b] OR (95% CI)	n (%)	Crude Model OR (95% CI)	Adjusted Model [b] OR (95% CI)
Pregnancy health care						
Public	4724 (97.7)	1.00	1.00	2889 (59.8)	1.00	1.00
Private	2956 (99.4)	3.59 (2.20-5.86)	1.84 (1.05-3.25)	1819 (61.1)	1.06 (0.96-1.16)	0.99 (0.89-1.10)
	p<0.001			*p=0.240*		
Prenatal visits						
≤2	43 (60.6)	0.02 (0.01-0.03)	0.03 (0.02-0.06)	32 (45.1)	0.48 (0.30-0.77)	0.58 (0.36-0.94)
3-6	801 (95.9)	0.25 (0.15-0.39)	0.37 (0.23-0.61)	463 (55.4)	0.73 (0.63-0.85)	0.80 (0.68-0.93)
7-9	3281 (99.1)	1.18 (0.72-1.92)	1.34 (0.82-2.19)	1946 (58.8)	0.83 (0.76-0.92)	0.87 (0.79-0.97)
≥10	3555 (99.0)	1.00	1.00	2267 (63.1)	1.00	1.00
	p<0.001			***p<0.001***		
Complications during pregnancy						
Yes	3113 (99.2)	2.67 (1.73-4.12)	2.08 (1.33-3.26)	2158 (68.7)	1.83 (1.66-2.01)	1.80 (1.63-1.98)
No	4567 (97.8)	1.00	1.00	2550 (54.6)	1.00	1.00
	p<0.001			***p<0.001***		

a – Excluding drugs from ATC code A11, ATC code A12 and ATC code B03;
b – Adjusted for education level, prenatal visits, complications during pregnancy, smoke before pregnancy and pregnancy health care.

The prevalence of drug use during pregnancy was higher among women aged 20-39 (98.5%), with more than 10-12 years of education (99.4% vs. <10-12years: 97.3%), and with a monthly income higher than 1500€ (99.2.0% vs. <1501: 98.2%). The prevalence was also more frequent among employed women (99.1% vs. 96.6%) and in those that had a higher childhood social status (99.2% vs. 98.1%). Primiparous women (98.9% vs.97.7%), those that had planned the current pregnancy (98.6% vs. 97.2%), chose private prenatal care (99.4% vs. 97.7%), had more than 7 appointments (99.0% vs. 93.2%) and had declared complications during pregnancy (99.2% vs. 97.8%) were also more likely to use drugs during pregnancy. The same was observed among women with a lower BMI (<25.0: 98.8% vs. ≥25.0: 97.7%) and non-smokers (98.6% vs. 97.6%).

Excluding supplements, only the educational level, the prenatal visits and complications during pregnancy remained associated in the same way as stated above. Most of the other characteristics are no longer associated with drug use. However, use of drugs was more frequent among women who had declared chronic diseases, had smoked before pregnancy and had not accepted the current pregnancy.

After adjusting the models, educational level, working condition, smoking habits before pregnancy, pregnancy health care system, prenatal visits and complications during pregnancy remained associated with drug use. The use of drugs during pregnancy was less likely to occur in less educated women (≤6 vs. >12 years: OR=0.49; 95%CI: 0.26-0.93). Housewives and unemployed women were less likely than employed women to use drugs during pregnancy (housewives: OR=0.27; 95%CI: 0.16-0.46, unemployed: OR=0.54; 95%CI: 0.34-0.86). Pre-pregnancy smokers were less likely to use drugs than non-smokers (OR=0.64; 95%CI: 0.44-0.95). Private prenatal care (OR=1.84; 95%CI: 1.05-3.25) and a higher number of visits increased the odds of drug use (vs. >10 visits: <3: OR=0.03; 95%CI: 0.02-0.06 and 3-6: OR=0.37; 95%CI: 0.23-0.61) as well as the occurrence of complications during the pregnancy (OR=2.08; 95%CI: 1.33-3.26).

After excluding supplements, chronic disease (OR=1.53; 95%CI: 1.39-1.68) and planned pregnancy (vs. planned: not planned but accepted: OR=1.31; 95%CI: 1.18-1.46, not planned and not accepted: OR=2.09; 95%CI: 1.43-3.06) became significantly associated with drug use, while the working condition and the health care system were no longer associated. In relation to smoking before pregnancy, smokers started to use drugs more frequently.

4. Discussion

Before pregnancy, the use of drugs was associated with the existence of a chronic condition. The use of drugs prior to pregnancy was linked with better social profiles when the supplements were included, while when they were excluded, it was associated with worse profiles. During pregnancy, despite the universal use of medicines, similar patterns were observed. The prevalence of drug use before and during pregnancy was 49.2% and 98.3%, respectively. Without the supplements the prevalence decreased to 34.9% before and 60.2% during pregnancy.

During pregnancy and including supplements, our results are in accordance with a French study (99%) (42), a German study (96.4%) (32), an English study (92.4%) (35) and two Brazilian studies (92.7%) (33) and (94.6%) (51). Excluding them, the overall rate of drug use during pregnancy decreased. These results are also of similar magnitude to one study from the United States (64%) (43), one from British Columbia, Canada (63.5%) (26).

According to our findings, there is an evident tendency for a greater use of drugs during pregnancy when comparing with the three months before pregnancy. The same is true of a study carried out in Serbia, in 2012 (25) and another from Scotland, in 2010 (31). There is some difficulty in comparing our results with other studies, as they may diverge in study design, study population, time period, drug exposure ascertainment method and even in drug classification systems. In our study, we take into consideration all the drugs that were reported by the women, it did not matter if the drug was prescribed or not. However, there are a considerable number of studies that used prescribed drugs (data bases) in order to analyse the consumption of drugs, however this method may overestimate the results, because there is no guarantee that the women took all of them.

It was verified that both before and during pregnancy drugs were mostly indicated by physicians. This is in accordance with a Brazilian study, where more than 80% of drugs used during pregnancy were recommended by a physician (51). In our study, a high percentage of drugs for which the recommendation is unknown was found, particularly before pregnancy, In relation to the drugs used before pregnancy, women were more likely not to remember the person who indicated the drug. However, during the pregnancy, although the same situation may have occurred, it is more likely that women were afraid or ashamed of saying who had indicated the

drug in cases when it was not the physician. As the questionnaire was performed after they had given birth, they may also have thought that if something had happened to the infant that it could be due to a drug that they had taken without medical advice.

Three months before pregnancy the most commonly used drugs by women belong to blood and blood forming organs category (B) and genito urinary system and sex hormones category (G) (19.1 and 22.8% respectively). The first one represents mainly the use of antianemic preparations (B03) which include folic acid and iron, and the second the use of sex hormones and modulators of the genital system (G03) where contraceptive drugs are included. The use of drugs from category B was higher among those women who planned the pregnancy and from category G was higher among women who did not plan the pregnancy (data not shown). Before pregnancy, more than 95.0% of the drugs from the subgroup B03 were folic acid alone or in combination. The proportion of women who used folic acid three months before pregnancy was lower taking into consideration that it is recommended to start this supplement before becoming pregnant. Periconceptional folate supplementation is effective against the development of neural tube defects (59). A study carried out in Australia showed that 29% of women took pre-pregnancy folic acid supplements, which is higher than our results (60). A French study showed that 14.8% of women took folic acid before pregnancy, which is lower but more similar to our findings (61).

The most frequently used drugs during pregnancy were those from alimentary tract and metabolism category (A) and blood and blood forming organs category (B) and were taken respectively by 66.4% and 95.4% of women, fundamentally because they contain the majority of the supplements taken during pregnancy. In category A, more than 40% of women used mineral supplements, mostly containing magnesium, which is often prescribed in pregnancy for cramps, preterm contractions and eclampsia (62-65). Vitamins and antiemetics are also included in this category. In category B, folic acid and iron are included, alone or in varying combinations, which are also commonly taken during pregnancy. The use of folic acid is usually recommended until 12 weeks of pregnancy, in order to prevent neural tube defects (61), while iron is usually used after the first trimester in cases of anaemia (66). As these two drugs may be used in different times during pregnancy, this can explain the small differences found in category B according to the trimesters of pregnancy. The use of drugs from category A and B is often recommended in order to improve maternal health as well as that of the foetus. The WHO recommends a daily dose of 400µg (0.4mg) of folic acid in pregnant women, however, in our country the used doses are much higher (67). For example, Acfol® and Folicil® which are the most used drugs contain 5mg of folic

acid. This difference in terms of dose is even more critical when women use one of the previous drugs plus a multivitamin which also include folic acid.

The use of drugs from genito urinary system and sex hormones category (G) during pregnancy decreased approximately 10%, due to no further utilization of contraceptives. However, some contraceptives were used during pregnancy, mostly during the first trimester, which seems to reflect the group of women who did not plan the pregnancy and only discovered the pregnancy after a few months. A wide use of analgesics and antipyretics during pregnancy was observed in our study, particularly acetaminophen, and this is consistent with the literature (25). Only this category of drugs is recommended during pregnancy with fewer restrictions (depending on the main substance), and as a consequence, women usually use them for various situations in an attempt to avoid the use of other drugs. Acetaminophen is commonly taken by pregnant women and frequently recommended by physicians to treat fever and pain during pregnancy (68). Numerous women have bacterial infections during pregnancy and, as a consequence they need to use antibacterials for systemic use (J01), otherwise it could lead to maternal and neonatal morbidity or mortality (69). In our findings, the prevalence of use of this subgroup was relatively high during pregnancy. These drugs were essentially used for urinary and dental infections. The prevalence of use increased in the second and third trimester of pregnancy. It may have occurred because, during the interview, women tended to report the most recent drugs used.

According to the ATC classification system, the duration of drug use during pregnancy was higher especially in the blood and blood forming organs category (B) and in systemic hormonal preparations, excluding sex hormones and insulins category (H). The first one represents the category where the preparations with folic acid and/or iron are included, as it is known that these two supplements are widely used during this period (56). Category H contains hormonal drugs that are usually used for a longer period of time and may indicate some chronic pathology. In this category, we essentially have drugs for thyroid disorders (propylthiouracil and levothyroxine sodium) and corticosteroids for systemic use. In relation to some of the most relevant ATC subgroups in our study, A04 was the one with the longest time of utilization; this represents the antiemetics used during pregnancy. This subgroup was especially used in the first trimester during pregnancy, which is in accordance with other studies (70, 71).

During pregnancy, a huge number of studies from developed countries showed low levels of use of category X (harmful to the foetus, the risk exceeds the benefit, and so this is not recommended

in pregnancy), but there are considerable variations (27, 31, 41, 42, 72, 73). In our findings category X level is slightly lower in relation to some studies. Some of the differences in the results may occur due mainly to different methodologies or study design (31). For example: the supplements and OTC drugs inclusion or not, the methodology of information collection, the selection of participants, among others. Studies using the FDA classification system show levels of category X between 0.4% of women in one US study (72) to approximately 4% in a Canadian study (27). In our study, it was found that 0.2% of women, (independently of the year in which drugs were classified according to their fetal risk) used non-recommended drugs (category X). Most drugs from category X were used during the first trimester of pregnancy, which could possibly indicate that the women had started taking the drug before knowing they were pregnant. In fact, the prevalence decreases to 0% in the second and third trimesters. This small difference may also reflect the sampling strategies used in this study, as it used data from a birth cohort, only live births were included. So, there could be some underestimation of the prevalence of drugs used during pregnancy, if some drug-induced congenital anomalies led to the termination of pregnancy. In our results, it was also verified that the use of drugs from category D (fetal evidence in animals, but the necessity may justify the risk) was higher than in some other studies. If we consider the 2004 or 2010 Infarmed publication, respectively, 6.8% and 8.7% of the women took at least one drug from category D. Most of the studies report values between, approximately 1% (41) and 5% (27) of women . However, a study conducted in France showed a greater percentage (59%) of drugs from category D, which differs immensely from other literature (42). The study authors did not explain why their results were so different from the others. However, the information was collected in 1996 and it may explain the results, because over the years some drugs may have changed category. If we consider studies undertaken using a different classification system, such as a study from Finland in 2004 (74), higher levels of usage of potentially dangerous drugs can be seen (20.4%). A further example from Denmark carried out in 1999, obtained results of 17.8% of women taking such drugs (30). It seems that the FDA classification system may be underestimating drug exposure.

The analysis of the maternal characteristics related to the use of drugs before and during pregnancy was performed including and excluding all the supplements. Before pregnancy the frequency of drug use decreased significantly at the same time as the educational level decreased. Primaparae and women with higher education tend to use drugs more often, which may be reflecting the inclusion of supplements in the analysis because they are more likely to follow guidelines. This is in accordance with a Brazilian study (33). Women who had reported chronic

diseases were also more likely to have used drugs. Excluding the use of supplements, we verified that the educational level and parity ceased to be associated and planning the pregnancy became relevant, however having reported chronic diseases remained associated in the same way as above. Women who suffer from chronic diseases usually have to continue to take certain drugs even when pregnant. Women who did not plan the pregnancy were more likely to take drugs more often in relation to those who planned to get pregnant. Women who plan pregnancies are usually more careful and try to avoid the use of some medication.

During pregnancy and including supplements, we verified that the use of drugs was associated with better life conditions. Women who chose the private health system and had more prenatal appointments used drugs more frequently. These two factors may be associated with better working conditions and/or a higher income. For example, there are companies that provide their employees with health insurance which may encourage women to choose private prenatal care. Drug use was also more common among women who had had some complication during pregnancy. Some complications may require the use of drugs. Pre-pregnancy smokers were less likely than non-smokers to use drugs. However, when we remove supplements from the analysis women who had smoked before pregnancy used drugs more commonly. Generally, tobacco is associated with several pathologies and as a consequence usually women who smoke have poor health (eg. respiratory problems) (75).

Strengths and Limitations

The fact that this study included all drugs used during pregnancy, including prescribed drugs and those used in self-medication, strengthened its external validity and increased its comparability. We considered all drugs reported by women whether or not they included vitamins, minerals, herbal or homeopathic products. We did not provide data on the latest two groups of drugs since it was not possible to classify them according to the ATC classification system or FDA fetal risk category (using Infarmed publications). However, they represented less than 1% of all drugs among of this group of women, and so their exclusion is not likely to bias the results.

There are several different methodologies for collecting data on drug use in pregnancy such as, extraction from medical reports, personal interview, self-administered questionnaires or a combination of more than one method. Data was collected in face-to-face interviews, which allowed for the detection of difficulties in understanding the items due to a poor educational level

or any grasp of the language, for example (76). Our interview was conducted between 24-72 hours after the delivery and so, it was expected that mothers would easily be able to remember what they had taken three months before pregnancy and during it. However, we cannot discard the possibility of memory bias, in which pregnancy complications or obstetric result may have changed the likelihood of drugs recall. In this sense we may have underestimated the true utilization of drugs, since the prevalence of adverse outcomes was not high.

Other factors may have affected the answers given. Our questionnaire was very long and took a great deal of time to be answered which could have induced fatigue in the women, particularly in this recent group of mothers (77, 78). This may have led to some involuntary omissions or incorrect details (e.g. dosage, frequency of usage etc.). It should also be taken into account that the mothers were going through a process of adaption to infant routines and the hospital environment.

Another point that should be taken into account is the type of questions that were used to evaluate drug exposure. In the questionnaire there were three questions about drug use; two related to the three months before pregnancy and one to the pregnancy itself. Besides the specific question on the pre-conception supplements that was used, the other two questions were open-ended due to logistical constrains. In opposition to closed questions on specific drugs or specific indications, this strategy may have resulted in the underestimation of drug recall, as responders we likely to be unwilling to take the time to answer them. It also increases the probability of differential recall of drugs for more severe or chronic conditions. However, this is less likely to have occurred with the drugs recall during pregnancy, because of the specificities of this period and the potential risk of drugs. In order to minimize potential under reporting, questions included some examples in brackets of the most commonly used drugs by women before and during pregnancy. This strategy is likely to have increased reporting of drugs that are usually more frequently forgotten (anticonceptionals, analgesics, sleeping pills or herbal medicines).

There were drugs that despite all our efforts we were unable to classify them, mainly because we could not find the drug that the women reported. Before pregnancy, about 6% of drugs (out of more than 5000) could not be classified according to the ATC classification system. During pregnancy it decreased to less than 2% (out of more than 27000). This may have underestimated the prevalence of some categories, but we expected bias to be minimal due to the low prevalence of unknown drugs. The classification according to the fetal risk led to a higher number of

unclassified drugs (about 10000). This group included multivitamins, mineral supplements such as magnesium and antiemetic drugs that are frequently used, but the compounds of which were not in the Infarmed publications lists (based on FDA classification). Despite being considered as safe to use in pregnancy, no evidence is available of their potentially harmful effect.

This study was undertaken using the FDA risk classification system which was not specifically created to identify teratogenic risk, although it is used to try to identify drugs which could potentially be dangerous during pregnancy (31). The FDA classification system has some limitations, since it may in some way oversimplify the difficulty in assessing the balance between damaging the foetus and keeping the mother healthy. The system can also be misconstrued as inducing the understanding of an increased risk in successive categories, or that drugs within the same category represent the same amount of risk. Perhaps due to these flaws it was suggested in 2008 that the FDA may cease to use the current classification system or update it in some way. Nonetheless, at the present time the system remains unchanged (25, 31, 79, 80). Despite all the limitations, this classification system is extremely useful for population-level research and it allows us to compare finding across countries.

Another particular strength was that our sample contained a high number of women due to an extremely high rate of acceptance. Moreover, the questionnaire was very thorough and therefore a wide variety of information was obtained. We used two Infarmed publications in order to classify drugs; this allowed us to see if there was any difference in drug allocation.

This study population included women who had a live birth in one of the six municipalities of Porto between 2005 and 2006 but, unfortunately no information was recorded in relation to women who had miscarriages or voluntary terminations. Knowing what those women had taken during and even before pregnancy would have been interesting and useful.

5. Conclusion

This study shows that even without drug safety evidence and considering the overall use, more than half of the women were using at least one drug before conception and most of them took drugs during pregnancy. Even excluding the use of supplements which are recommended in the guidelines, the frequency of use was high. However, the levels of potentially harmful drugs are very low. Our study also shows that the use of drugs increases during the pregnancy.

The use of drugs was associated with a pre-existing chronic condition before pregnancy. There was also an association between pre-conceptual drug use and better social status when the use of supplements is included. When the supplements are excluded, drug use becomes associated with lower social status. Similar patterns were found during pregnancy, despite the universal use of medicines.

These results enhance the need for pharmacovigilance systems to evaluate the post marketing period in order to estimate the risk-benefit profile of drugs in pregnant women. Priority research should be performed on the most widely used drugs in pregnancy because of the unknown risks.

For some drugs that are commonly used by pregnant women maybe it is time to start thinking about performing trials on this particular population. This is a controversial topic however, allowing pregnant women to take drugs without having information does not seem appropriate or safe. But whether the benefits of including pregnant women in clinical drug trials outweigh the risks is up for debate.

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7. Annex 1

Detailed description of the ATC classification system up to the second level (45)

A - Alimentary tract and metabolism

A01-Stomatological preparations

A02-Drugs for acid related disorders

A03-Drugs for functional gastrointestinal disorders

A04-Antiemetics and antinauseants

A05-Bile and liver therapy

A06-Drugs for constipation

A07-Antidiarrheals, intestinal antiinflammatory/antiinfective agents

A08- Antiobesity preparations, excl. Diet products

A09-Digestives, incl. Enzymes

A10-Drugs used in diabetes

A11-Vitamins

A12-Mineral supplements

A13-Tonics

A14-Anabolic agents for systemic use

A15-Appetite stimulants

A16-Other alimentary tract and metabolism products

B - Blood and blood forming organs

B01-Antithrombotic agents

B02-Antihemorrhagics

B03-Antianemic preparations

B05-Blood substitutes and perfusion solutions

B06-Other hematological agents

C - Cardiovascular system

C01-Cardiac therapy

C02-Antihypertensives

C03-Diuretics

C04-Peripheral vasodilators

C05-Vasoprotectives

C07-Beta blocking agents

C08-Calcium channel blockers

C09-Agents acting on the renin-angiotensin system

C10-Lipid modifying agents

D - Dermatologicals

D01-Antifungals for dermatological use

D02-Emollients and protectives

D03-Preparations for treatment of wounds and ulcers

D04-Antipruritics, incl. Antihistamines, anesthetics, etc.

D05-Antipsoriatics

D06-Antibiotics and chemotherapeutics for dermatological use

D07-Corticosteroids, dermatological preparations

D08-Antiseptics and disinfectants

D09-Medicated dressings

D10-Anti-acne preparations

D11-Other dermatological preparations

G - Genito urinary system and sex hormones

G01-Gynecological antiinfectives and antiseptics

G02-Other gynecologicals

G03-Sex hormones and modulators of the genital system

G04-Urologicals

H - Systemic hormonal preparations, excl. Sex hormones and insulins

H01-Pituitary and hypothalamic hormones and analogues

H02-Corticosteroids for systemic use

H03-Thyroid therapy

H04-Pancreatic hormones

H05-Calcium homeostasis

J - Antiinfectives for systemic use

J01-Antibacterials for systemic use

J02-Antimycotics for systemic use

J04-Antimycobacterials

J05-Antivirals for systemic use

J06-Immune sera and immunoglobulins

J07-Vaccines

L - Antineoplastic and immunomodulating agents

L01-Antineoplastic agents

L02-Endocrine therapy

L03-Immunostimulants

L04-Immunosuppressants

M -Musculo-skeletal system

M01-Antiinflammatory and antirheumatic products

M02-Topical products for joint and muscular pain

M03-Muscle relaxants

M04-Antigout preparations

M05-Drugs for treatment of bone diseases

M09-Other drugs for disorders of the musculo-skeletal system

N -Nervous system

N01-Anesthetics

N02-Analgesics

N03-Antiepileptics

N04-Anti-parkinson drugs

N05-Psycholeptics

N06-Psychoanaleptics

N07-Other nervous system drugs

P - Antiparasitic products, insecticides and repellents

P01-Antiprotozoals

P02-Anthelmintics

P03-Ectoparasiticides, incl. Scabicides, insecticides and repellents

R - Respiratory system

R01-Nasal preparations

R02-Throat preparations

R03-Drugs for obstructive airway diseases

R05-Cough and cold preparations

R06-Antihistamines for systemic use

R07-Other respiratory system products

S - Sensory organs

S01-Ophthalmologicals

S02-Otologicals

S03-Ophthalmological and otological preparations

V - Various

V01-Allergens

V03-All other therapeutic products

V04-Diagnostic agents

V06-General nutrients

V07-All other non-therapeutic products

V08-Contrast media

V09-Diagnostic radiopharmaceuticals

V10-Therapeutic radiopharmaceuticals