Medications in pregnancy: challenges and concerns

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Pregnancy is a physiological condition in which drug treatment is a particularly delicate issue, since many medications can cross the blood - placental barrier and potentially cause harm to the fetus. In addition, the physiological changes in pregnancy can negatively affect the pharmacokinetics of medications used. On the other hand, total avoidance of pharmacological therapy in pregnancy will of course be unsafe for those women who enter pregnancy with medical conditions that require treatment, while therapy is evidently also imperative whenever new medical problems develop during pregnancy or old ones are exacerbated.

In the late 1950s and early 1960s, more than 10,000 children in 46 countries were born with defects such as phocomelia as a consequence of thalidomide use in the first 42 days of gestation. From about 1940 to 1971, diethylstilbestrol (DES) was given to pregnant women in the mistaken belief it would reduce the risk of pregnancy complications and fetal loss. In 1971, DES was shown to cause clear cell carcinoma, a rare vaginal tumor, in women who had been exposed to this drug in utero. Such catastrophic events led the United States Food and Drug Administration (FDA) in 1979 to establish strict regulations regarding the use of medications in pregnancy and requiring demonstrations of safety and efficacy of any drug before it becomes commercially available. Medications were divided into 5 categories, defined according to the reliability of safety documentation, ranging from category A which includes drugs for which adequate and well - controlled studies have failed to demonstrate any risk to the fetus, to category X including medications for which studies have demonstrated positive evidence of human fetal risk and where the risks of using the drug in pregnant women clearly outweigh potential benefits (including medications contraindicated in women who are or may become pregnant, but also those which have no indication for use in pregnancy). It should be noted that the new FDA pregnancy and lactation labeling rule, effective as from June 30, 2015, has removed pregnancy letter categories A, B, C, D and X and made historic changes in prescription medication labeling requirements (Information available at: https://www.federalregister.gov/articles/2014/12/04/2014 - 28241/content - and - format - of - labeling - for - human - prescription - drug - and - biological - products - requirements - for).

Despite the massive accumulation of data, the situation remains dis-

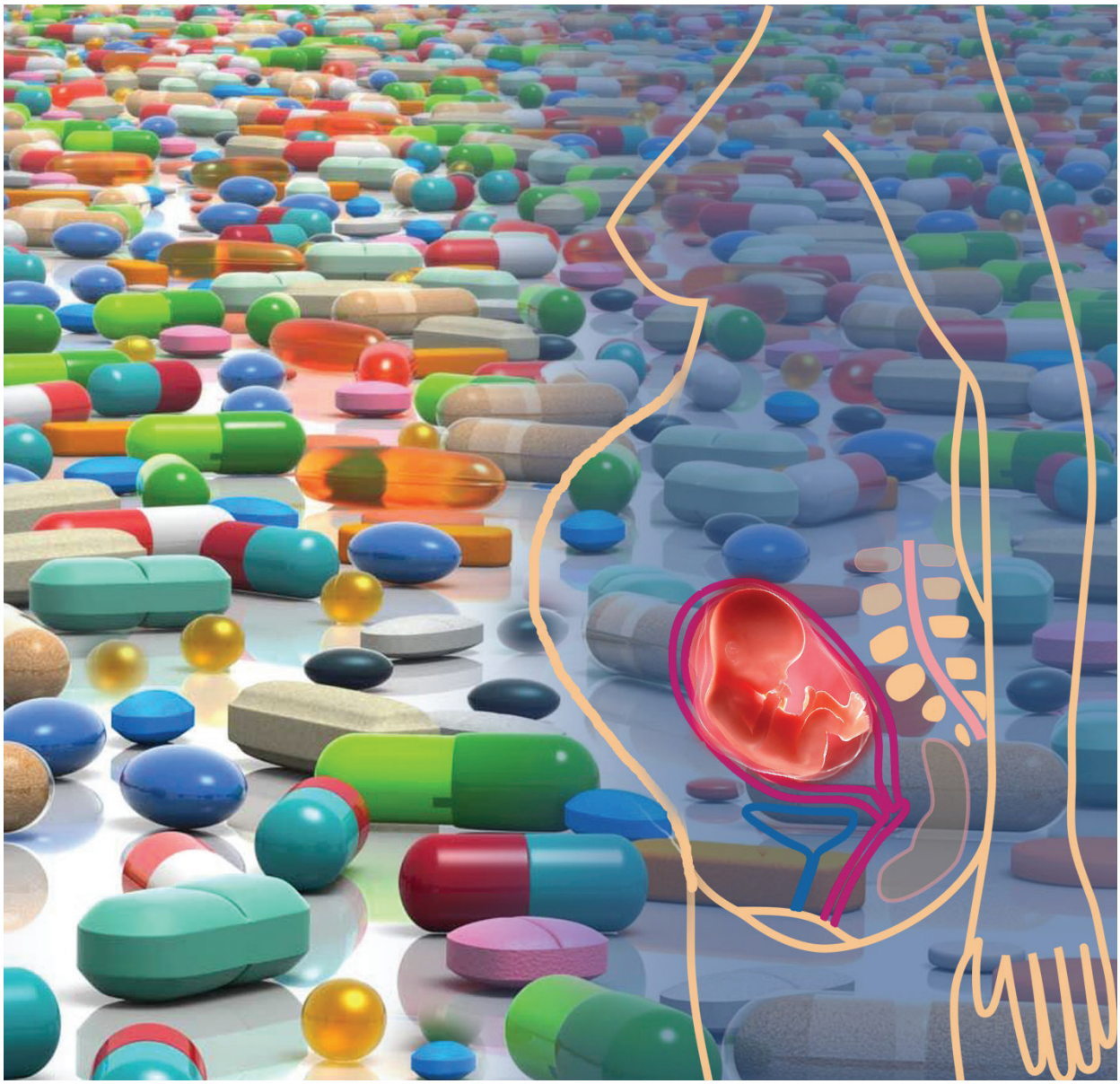

Figure. The risks associated with medications in pregnancy represent a major public health concern

tressingly unclear. A study in 2001 found that there was insufficient information concerning the risk of more than 90% of medications approved by the FDA between 1980 and 2000 when taken during pregnancy. Furthermore, it was calculated that the mean time from the approval of a medication to ascertainment of a definite risk to pregnancy was 27 years. Meanwhile, the proportion of pregnant women who need drug treatment due to various chronic diseases and pregnancy - related complications is continuously on the rise on account of increasing maternal age.

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marily because pregnancy is very common among young women. Using the official national data, it is estimated that on any random day in Greece during 2013, excluding spontaneous miscarriages, stillbirths and induced abortions, 1.7% of women aged 15 - 44 were pregnant, this proportion rising to 6.7% among women aged 30 - 34 years (approximately 1 out of 15). There are besides a large number of women who are on a medication(s) in the early weeks of pregnancy before realizing that they are pregnant. Meanwhile, in the United States, more than 90% of pregnant women take prescription or over - the - counter drugs or use social drugs such as tobacco, alcohol or illicit drugs at some time during pregnancy, while from 1976 to 2008 first - trimester use of prescription medication in the US has increased by more than 60%. Notably, one review found that a teratogenic risk in human pregnancy was undetermined in 98% of 172 medications approved by the FDA between 2000 and 2010.

Today, the majority of pregnant women use prescription medications - either without the knowledge of their attending obstetrician - gynaecologist or dispensed without sufficient information - so that an extremely large proportion of pregnancies are exposed to drugs not recommended during pregnancy. The largest relative study, conducted by Kristin Palmsten and colleagues and published in the Obstetrics and Gynecology journal (Obstet Gynecol 2015;126:465 - 73), included more than 1,100,000 pregnant women enrolled in the United States Medicaid program from 2000 to 2007. The researchers reported that at least one prescription medication was dispensed in 83% of pregnant women. The most commonly dispensed class of medications during pregnancy was antibiotics, with a proportion of almost 50%. The 5 most common medications during pregnancy included nitrofurantoin (22%) (category B), metronidazole (19%) (category B), amoxicillin (18%) (category B), azithromycin (17%) (category B) and promethazine (14%) (category C). Promethazine and nitrofurantoin were the commonest drugs prescribed in the first trimester, while nitrofurantoin and metronidazole were the commonest during the second and third trimester. Proportions were highest among women younger than 20 years. Excluding fertility treatments, 42% of the cohort had at least one dispensing for a D or X medication during pregnancy, with codeine (12%) and hydrocodone (10%) being the most common D category medications. The researchers specifically mentioned several among 180 different D or X category medications dispensed during pregnancy, women aged 25 - 29 years having the highest proportion of D and X medications. The proportion of dispensed X category medications increased by one - third, from 2001 to 2007 (from 4.1% to 5.4%). Another study which included more than 32,000 pregnancies in the Netherlands found that in almost 18% of the pregnant women, at least one medication associated with a teratogenic mechanism was dispensed in the first trimester.

Conducting randomized controlled trials (RCTs) to investigate medication safety in patients who are pregnant or breast - feeding is considered unethical. Therefore, medication safety information in pregnancy is at present obtained through case reports, epidemiological studies and animal studies, all of which have important limitations. In many developed countries, registration systems have been set up to collect information about all the medications used by pregnant women. The most systematic and thorough registration of medications in pregnancy at a national level is the Danish Medical Birth Registry which has monitored all pregnancies and births in Denmark since 1973. The analysis of these data has provided the most valuable information to date on the safety of a great number of medications in pregnancy and has produced papers published in the world's leading medical journals, such as the New England Journal of Medicine and the Journal of the American Medical Association (JAMA). However, despite the enormous number of pregnancies investigated, documentation of the safety of a drug in pregnancy is difficult, since even a small increase

in adverse effects could have major public health implications.

For example, more than 50% of pregnant women take medication for morning sickness. If only 30% of them take such a drug, that could carry a 5% chance, non - detectable by even large studies, of increasing the risk of congenital malformation, this would result in almost 1,000 more birth - defect cases annually in the United States alone. The effect also depends on the developmental stage during which the drug is administered, or an agent may be teratogenic only over a particular dose level (dose - dependent risk). Another methodological challenge in these studies is the potential association with birth defects of the disease for which the drug is used (confounding by indication). For example, if women with depression are more likely to have children with autism, a false association between selective serotonin reuptake inhibitors (SSRIs) use and autism will be present in an observational study.

Bearing in mind that balancing risks and benefits in medications prescription during pregnancy is one of the classical problems in medicine in general, but perhaps especially in obstetrics, prescription for pregnant women is undoubtedly a major area of application for the Hippocratic aphorism "ὠφελέειν, ἢ μὴ βλάπτειν" (to help, or at least, to do no harm). Considering all the above, it is evident that obstetricians need to be thoroughly informed and meticulous in administration of drugs in pregnancy, while it is also their duty to be in a position to counsel doctors of other specialties regarding the safety of medications administered to pregnant women. In our country, we call upon all Greek obstetricians to abide by these recommendations while also scrupulously recording and monitoring the use and the side effects of drugs during pregnancy and lactation.