Clotrimazole, Pregnancy and Endocrine Disruption: A Narrative Review

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Received date: February 12, 2021; Accepted date: March 11, 2021; Published date: March 16, 2021

Abstract

Background: Clotrimazole is an antifungal drug commonly used in human medicine. It is considered to be safe in pregnancy. Besides this medical assumption ecotoxicology has developed over the last years an awareness of pharmaceuticals which have been detected in surface waters and are of concern for the biosphere. Some of those drugs are endocrine disruptors. So is clotrimazole.

Methods: Selective internet research on this subject incorporating medical and ecotoxicological positions.

Conclusions: Ecotoxicology and human medicine postulate divergent positions about the harmful effects of clotrimazole. Medicine bases its assumption on thousands of healthy newborn babies whose mothers were treated with clotrimazole during pregnancy. This argument is easy to refute as clotrimazole is an endocrine disruptor and possible consequences of exposure during sensitive periods of pregnancy will only show up much later in life. As a result medicine is challenged to incorporate ecotoxicological concerns into its advice for pregnant women.

Keywords: Clotrimazole, pregnancy, endocrine disruption

Introduction

Clotrimazol is an antifungal drug used in gynaecology and obstetrics since the early 1970’s. It is commonly sold over the counter being more akin a consumer health product than a pharmaceutical. Various advisory web sites including NICE in the UK [1], CDC in the United States [2] and embryotox in Germany [3] recommend its use during pregnancy. Current medical guidelines similarly allow antifungal treatment with clotrimazole during pregnancy [4-6]. These guidelines rely on studies examining thousands of newborn babies who did not show any structural abnormalities after drug exposure during their foetal life [7,8]. However, this does not take into account current ecotoxicological knowledge about the endocrine-disrupting properties of clotrimazole. The potential damage to an unborn baby might appear much later in life and not show up shortly after birth. This narrative review compiles the different and divergent positions of ecotoxicology and medicine regarding clotrimazole and related antifungals.

Methods and Results

Some few years ago I developed an interest in ecotoxicological matters, triggered by discussing different health phenomena with non-medical friends. We talked about the apparent increase in infertility, the female-dominated transgender phenomena or the increase in behavioural changes. As expected, there were no conclusive answers. My first ecotoxicological study addressing the harmfulness of clotrimazole was a chance finding scrolling the Internet late at night – I am admittedly something of a nerd. Some months later, triggered by a review article in a well-established German medical paper [5], my interest returned and I started to search Pubmed using the terms “endocrine disruption”, “clotrimazole”, “aromatase inhibition” and “steroidogenesis”. Beside
this medical search engine, I was scrolling through EPA’s CompTox Medical Dashboard. The medical literature relating to clotrimazole mainly refers to quotations from the above-mentioned medical guidelines. As a result, I have read and studied 89 different publications, mainly from ecotoxicology but also from neuroanatomy and of course obstetrics.

Clotrimazole: views of ecotoxicology

Ecotoxicology is a multidisciplinary science studying effects of toxic substances on living organisms. Pharmaceuticals end up in the environment after use in humans as waste water treatment plants are unable to extract them. Various drugs like clotrimazole have been detected in surface waters and therefore became an ecotoxicological issue.

Since the early 2000s ecotoxicology has proved that clotrimazole is an endocrine disruptor and exerts damaging effects on vertebrae. The harmful action is due to a side effect – the unspecific inhibition of aromatase [9]. This enzyme converts male androgens into female oestrogens and plays a pivotal role in sexual differentiation. Furthermore, clotrimazole inhibits sterol – 14 – alpha - demethylase. In mammals this enzyme produces MAS; meiosis-activating steroids, which modulate germ cell development [9]. The enzyme aromatase is found in different vertebral tissues, mainly where a sex differentiation happens. This includes not just the ovaries and testicles but also the adrenal cortical gland, the placenta and the brain. Bickley et al. [10] and Brown et al. [11] described reduced male fertility and a sex skew towards the male in zebrafish when exposed to low levels of clotrimazole. Baudiffier et al. [12] demonstrated that low dose clotrimazole altered testicular physiology in zebra fish raising concerns on reproduction. Huahong S [13] proved that low levels of chronic exposure to clotrimazole reduce the growth and viability of larvae from Xenopus tropicalis, the western clawed frog. Other experiments on this laboratory animal have described the modulation of gonadal and brain aromatase in clotrimazole-exposed larvae [14]. There is an abundance of literature using cell culture experiments and biochemical assays with human aromatase, proving that clotrimazole affects steroidogenesis [15-17]. Munkboel et al. [17] used recombinant aromatase assays as well as H295R cell culture to show that clotrimazole and related antifungals exert endocrine disruptive effects even in therapeutic levels. The authors explicitly stated that, “... this raises concern for endocrine related effects in patients using azole antifungal drugs, particularly when taken during sensitive periods like pregnancy”.

Inhibition of brain aromatase – views of neurobiology

As early as 1994, Connolly et al. [18] described brain areas in foetal guinea pigs with aromatase activity, such as the amygdala and the preoptic nucleus. The aromatase activity was highest in early gestation and declined with further intrauterine development. They therefore suggested that these brain areas develop under the influence of oestrogen and develop sex-dependently. Further animal studies have shown altered reproductive behaviour when aromatase inhibition occurs during early gestational stages [19]. In recent years, neurobiology has depicted brain areas with aromatase activity which does not serve reproductive behaviour. Here, oestrogens act as signalling neurotransmitters. These areas are the basolateral parts of the amygdala, which are known as key structures of the fear circuit. Bender et al. [20] used the medical aromatase inhibitor letrozole, showing that its use alters the synaptic plasticity of the basolateral amygdala – but only in female rats, not in males. He therefore suggests that oestrogen signalling of special brain neurons is regulated sex-dependently, presumably via mechanisms established during sexual determination.

Clotrimazole: medical views

Clotrimazole is an antifungal drug used for skin rashes and the treatment of vulvovaginal candidiasis, VVC or commonly called thrush. Candida is a yeast which can colonize the vagina, either asymptomatically or causing symptoms such as pruritus and vaginal discharge. It happens when the naturally balanced microflora is disrupted and the yeast multiplies, for example after treatment with antibiotics or in the case of diabetes mellitus. Clotrimazole is a non-prescription drug and comes as vaginal creams or vaginal pessaries. The drug acts locally, but some of it is resorbed through the special inner lining of the vagina. The clotrimazole concentration in serum is 30 mg/l, when using a 100 mg pessary [21]. As a relatively small molecule of 345 Dalton clotrimazole is expected to pass the placental barrier. It is not known at all whether clotrimazole applied vaginally concentrates in the womb, entering via the cervical canal. In theory, if 0.001% of the individual vaginal dose of 500 mg were absorbed, relevant concentrations of toxic substances would develop in the amniotic fluid. This is at least thinkable, as major concentrations of clotrimazole remain vaginally even 72 hours after using a 500 mg pessary [21]. Furthermore, there is the so-called First Uterine Pass Effect [22-24], which says that chemical substances
brought into the vagina preferentially distribute in the uterus – and thus in the unborn baby. This effect optimizes reproduction and is used medically in pregnant women to start labour with prostaglandin pessaries. It must be borne in mind that the serum concentration of drugs applied vaginally is much lower than the concentration in the womb. The potential toxic damage of a drug used vaginally is therefore much greater.

**Clotrimazole and current guidelines in medicine**

Current medical guidelines [4-6] specifically advise that clotrimazole can be used during pregnancy. They refer to studies [7,8] which did not detect any structural abnormalities in newborn babies after their mothers had been treated with this drug during pregnancy. According to the current guidelines of the German Society of Gynaecology and Obstetrics [4], vulvovaginal candidiasis (VVC) should be treated with clotrimazole. The text assumes the following:

1. Repeated candidiasis is a risk factor for preterm birth
2. Treating candidiasis reduces the risk of preterm birth

Regarding the first point, the literature looking at candidiasis and preterm birth is inconsistent. A current meta-analysis [25] does not see any significant relation between the two and was not quoted in the current guidelines of September 2020. The literature [26-28] on which the recommendation is based does not support the assumption. Farr et al. [26], for example, describes a moderate increase in preterm births in women with recurrent candidiasis. It is not clear if there is a direct link or if both phenomena are linked by an independent different cause. The terse description of the patients’ characteristics suggests that the two groups cannot be compared.

Regarding the second point, a large retrospective Hungarian study [29] described a reduction in preterm births in women treated with clotrimazole. The study does not give any explanation as to why this effect might have happened. I follow the explanation by Kragie et al. [15] that the inhibition of placental aromatase hampers placental function and delays parturition. This hypothesis is supported by a small but methodically sound Australian study [28] investigating 500 pregnant women who had no symptoms. Roughly 20 per cent of them were carrying Candida and were divided into two equal groups of 50 women in each study arm who either were receiving clotrimazole as a vaginal treatment or were left untreated. Table 1 shows a small but not meaningful reduction in preterm birth in the clotrimazole treatment group, two instead of three women delivered pre term. The results further show that sixteen instead of eleven women needed labour induction because of delayed parturition. Consequently, there is a higher number of overweight babies in the clotrimazole group.

**Discussion**

My narrative review relies on numerous ecotoxicological studies dealing with harmful effects on vertebrae resulting from clotrimazole as an endocrine disruptor. These damaging effects have been described at exposure concentrations lower than therapeutic serum levels [17]. I have compared these statements with current medical guidelines advocating the use of clotrimazole during pregnancy. My review does not claim to be a comprehensive summary of ecotoxicological knowledge, and I also admit to not being a biochemistry specialist understanding the minutia of biochemical assays. I felt more at ease assessing the medical guidelines in obstetrics promoting the use of clotrimazole during pregnancy and stating its safety due to the non-appearance of structural defects at birth following clotrimazole exposure. Obviously, there is a logical gap between ecotoxicology and medicine. Clotrimazole is an endocrine disruptor. Harmful effects to an unborn baby are hardly detectable at birth. The following items have to be taken into account:

Clotrimazole impairs the synthesis of oestrogens by inhibiting aromatase. This might be compensated for via the hypothalamus–pituitary gland – gonadal axis. However, we do not know if this compensatory action happens, if it is sufficient, or how long it lasts. We also cannot know if this reaction is excessive or what other mechanisms it triggers.

Human aromatase and aromatase of other vertebrae are similar but not identical. The same applies to aromatase and its tissue-specific iso-enzymes, including its promoter areas, when comparing different individuals. Some individuals might thus not be influenced by clotrimazole, while others are. Harmful actions of clotrimazole therefore depend on the genetic make-up of the individual.

The prenatal shaping of our personality, including reproductive behaviour and mental traits, happens in distinct time periods. Potential damage to an unborn baby through endocrine disruptors such as clotrimazole will depend on the time of exposure.

The potential consequences of clotrimazole exposure
might include male/female infertility, mental health problems, transgender phenomena, altered pubertal development and prolonged pregnancy with delayed parturition [28].

Adverse effects of intrauterine exposure with an endocrine disruptor like clotrimazole are hardly to pinpoint as they happen stochastically and emerge with a long latency. Bluntly spoken, no couple brings the old age mother to the fertility clinic, who might remember a full antenatal history of endocrine disrupting exposure some thirty years earlier.

Clotrimazole is only one of many endocrine disruptors which accompany our life and might exert similar effects. To mention a few, these include plasticisers, tablet coatings, preservatives in personal care products such as creams and toothpaste, coating materials, pesticides used in agriculture and other medications. Similar effects might be expected from ibuprofen [30], SSRI antidepressants [31] and progesterone.

Damage effects of different endocrine disruptors might increase with cumulative exposure to other chemicals. Exposing rats that are pregnant to mixtures of 4-10 endocrine disruptors can have adverse effects, yet each chemical is ineffective at an individual level [32].

**Summary**

Clotrimazole and related antifungals are drugs commonly used in obstetrics leading to substantial drug exposure of an unborn child. Ecotoxicology identifies clotrimazole as an endocrine disruptor which can harm the fetus. There is obviously a knowledge gap and ecotoxicological statements have not been so far translated into medical knowledge. Following the precautionary principle clotrimazole should not be used during pregnancy, especially as there are proven harmless alternatives.

Medicine is challenged to incorporate ecotoxicological statements about clotrimazole into its drug safety advice. Future research of both sciences should refute or strengthen above mentioned serious reservations and might identify further substances which harm our health long term too.

**Conflict of interest**

None
Funding
None

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