Holoprosencephaly in clomiphene-induced pregnancy: a possible association? A case report and literature review

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Summary

Clomiphene is widely used for inducing ovulation. Evidence for congenital abnormalities, in particular central nervous system defects (CNS-D) and in babies born from clomiphene-induced pregnancies is conflicting. The authors report a case of holoprosencephalia (HPE) in a fetus delivered from a mother receiving clomiphene.

Key words: Pregnancy; Malformation; Clomiphene; Holoprosencephaly.

Introduction

Holoprosencephaly (HPE) is a complex brain malformation resulting from incomplete cleavage of the prosencephalon, occurring between the 18th and the 28th day of gestation and affecting both the forebrain and the face. It is estimated to occur in one in 16,000 live births [1]. During early embryonic period, the frequency is one in 250, but progressively declines because of high mortality rates [2]. The term was first used in 1963 to describe a spectrum of malformations which have, as their common finding, failure of the proper formation of midline structures of the forebrain [3]. The range of expression varies from mild forms, where the right and left ventricles are separated, but there is continuity across the frontal cortex, to severe forms, where there is a single brain and no interhemispheric fissure (alobar holoprosencephaly). The severe forms are generally associated with facial deformities such as anophthalmia, cyclopia, and the presence of a proboscis [4].

Case Report

A 29-year-old infertile woman was treated with clomiphene for two consecutive cycles starting on day two of her menstrual cycle (50 mg for five days). After the second cycle of clomiphene, she became pregnant. The initial pregnancy course was normal and no illness or drug consumption were reported. An ultrasound at 20 weeks of gestation gave unclear results for brain malformations; the echographic examination repeated after six weeks showed cerebral malformations. At 32 weeks of gestation, the patient legally terminated the course of pregnancy: she delivered a 1,690 g fetus affected by holoprosencephaly and cleft lip and palate. Genetic consultation revealed a normal fetal karyotype; the familiar history was negative for holoprosencephaly. TORCH infection during the first trimester was excluded. The molecular genetic diagnosis was not pursued due to its high cost and because it was not expected to provide a reliable prognosis for the family.

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Discussion

The causative factors of HPE are numerous, of which chromosomal disorders account for no more than 40% to 50% of cases, with a higher prevalence observed in trisomy 13, trisomy 18, and triploidy. Mutations seen in the putative genes account for about 28% of all HPE cases. HPE can also be associated with several multiple malformation syndromes with a normal karyotype, as CHARGE syndrome, Smith-Lemli-Opitz syndrome, and others [5]. The remaining cases of HPE are thought to be related to maternal diseases and/or exposure to teratogens: risk factors include maternal diabetes [6], maternal alcoholism [7], and prenatal exposure to drugs, such as retinoic acid [8], antiepileptic drugs [9] or cholesterol biosynthesis inhibitors [10]. Moreover, cytomegalovirus [11], toxoplasma [12], and rubella [13] have been suspected to be involved in the pathogenesis of the malformation. Other anectodal reports have suggested a possible association between HPE and/or cyclopia and in utero exposure to sulfasalazine [14], salicilates [15], estroprogestins [16] or misoprostol [17].

In the past decades, a causal association between CNS-D and clomiphene has been suggested. In 1973, Dyson and Kohler described two patients who delivered infants with anencephaly and spina bifida following treatment with clomiphene [18]. Since this initial report, several similar observations have been reported [19-21]. To the authors' knowledge, no cases of HPE associated to clomiphene in utero exposure have been reported.

The association between use of clomiphene and HPE could be considered unlikely if the active substance is not present during the first weeks of embyogenesis. Geier *et al*. demonstrated the absence of clomiphene and/or its metabolites during organogenesis in the blood of patients previously treated with clomiphene [22]. By contrast, other studies reported that a small amount of clomiphene and its metabolites excreted in the urine and in the feces may be detectable for six weeks after treatment [23]. Moreover, using a mouse model, Dziadek reported an increased risk of exencephaly in the offsprings of females injected with clomiphene before ovulation in doses similar to those used in humans [24].

Clomiphene is excreted principally through the intestine.

Five days after oral administration, 51% of the administered dose is excreted. However, some clomiphene and its metabolites are detectable for six weeks in biological samples, suggesting an enterohepatic recirculation of the drug and its metabolites. Serum concentrations of zuclomiphene (cis-isomer of clomiphene) remains at least ten percent of peak levels 28 days after ingestion of a single 50 mg tablet. Therefore, repeated administration of a single 50 mg tablet at 28-day intervals may undergo accumulation and the effects of these doses may be cumulative [25]. For this reason, clomiphene may be more effective in inducing ovulation during the second and later cycles of treatment athough the dose administered remains the same. This accumulation justifies the presence of clomiphene even after the "all or nothing" period with possible unwanted effects in some patients.

Studies investigating the association between neural tube defects and clomiphene use do not provide conclusive results. Some epidemiological studies suggested that clomiphene did not appear to substantially contribute to the occurrence of isolated CNS-D [26, 27]. A pooled analysis of all of these studies on clomiphene and CNS-D showed a prevalence ratio of 1.08 (95% CI 0.76 - 1.51) and the authors concluded that an increased risk of CNS-D due to clomiphene could not be ruled out, although any such elevation seemed likely to be less than twofold [28]. A similar result (OR 4.5, 95% CI 0.7 - 26.7) has been reported from other authors after adjustment for confounders, although the initial crude OR was 6.4 (95% CI 1.3 - 31.4) [29]. Finally, in a recent population-based, multi-site case-control study, Reefhuis *et al*. identified association between use of clomiphene and CNS-D like anencephaly and showed an adjusted OR of 2.3 (95% CI 1.01 - 4.07), as well as a significant association with cardiovascular and other malformations [30].

Conclusion

In conclusion, there are no current clear elements to establish if clomiphene therapy may be a risk factor for holoprosencephaly. The authors' experience adds a further possible case of central nervous system defects observed after clomiphene use to those already published. Larger studies are needed to better understand if clomiphene has some teratogenic potential.

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