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Letter to the Editor

Should We Really Screen for Genital Variants Before Birth?

Prenatal diagnosis of congenital defects is now common and some fetuses may benefit from a prenatal intervention or a well-organized delivery in an optimal environment with medical and surgical capabilities. Some defects are worth screening for since they may reveal severe, untreatable syndromes with severely altered quality of life that may justify pregnancy termination according to local legislation [1].

Atypical genitalia development (AGD) belongs to the spectrum of fetal defects that can be detected before birth. These include hypospadias, epispadias, clitoromegaly, and other complex conditions for which the determination of sex remains uncertain. Prenatal detection of these defects has been increasing in recent years thanks to technological advances in ultrasound imaging and the increasing experience of prenatal sonographers. In contrast to other defects, prenatal diagnosis of genital variants is a part of a totally different and new landscape and this screening raises specific questions far beyond technical progress.

First, objective data on the performance of prenatal screening for genital defects are still lacking. The sensitivity of this screening has not been evaluated to date and is probably far lower than for detection of other abnormalities [2]. The sensitivity may depend on the severity of the underlying defects, but minor defects such as anterior hypospadias are most often missed even though they are now more frequently detectable [3]. The reliability and reproducibility of this screening are also sparsely reported. The correlation between prenatal and postnatal findings remains limited and a significant number of diagnoses before birth prove to be erroneous. For instance, the absence of clear borders between clitoromegaly and micropenis before birth is symptomatic of possible confusion. Validated prognostic factors that should constitute the basis for efficient prenatal diagnosis and that should drive parental counseling are still under study [4].

Second, the extent of the prenatal evaluation is controversial in the case of ADG detection. Additional explorations such as hormone measurements in the amniotic fluid and genetic testing on fetal samples or maternal blood may be proposed. Their interest is in fact debatable. On one hand, a precise molecular diagnosis may help to predict the long-term prognosis for a fetus with defects, such as the growth potential of the penis for a mutation of the androgen receptor. On the other hand, most 46,XY disorders of sexual development remain unexplained [5], the correlation between phenotypes and genotypes remains limited for most genes, and online databases often lack data on long-term outcomes. There is thus no consensus on whether these tests should be discussed with the parents and performed until they have been proven to be pertinent.

The final aim of any prenatal diagnosis is to improve the quality of life of the child or their survival rate in the case of a life-threatening condition. Such benefits are still difficult to establish for the most frequent and severe urological defects such as posterior urethral valves. The benefit of identifying a genital variation and its etiology before birth is even more disputable since no specific prenatal treatment will be proposed, except for some cases of familial congenital adrenal hyperplasia. Prenatal diagnosis of ADG may still help in providing better parental information, planning a delivery in a specialized tertiary center, and organizing a quick multidisciplinary work-up at birth. But we are now unable to determine if this improves the postnatal management of these children and we are even further from demonstrating any enhancement of their quality of life.

Prenatal diagnosis of ADG may also add confusion to the complex topic of genital variations. Management of children with atypical genitalia has dramatically evolved. From a technical point of view, next-generation sequencing methods provide a better and deeper understanding of the pathways of gonadal determination and genital differentiation. From a societal point of view, new ethical and legal issues challenge the classical options for these children and their families, including early masculinization or feminization procedures and treatment. A nonsurgical option has been proposed to ensure later participation by the child in the decision process even if long-term studies of both psychological consequences and postoperative outcomes for this choice are lacking. Transposing these questions to the prenatal period adds another level of complexity, including the rights of the fetus and those of the parents as well as political considerations.

Last, prenatal diagnosis of genital variation may be counterproductive in current practice and may even cause inextricable situations. Because of its rarity, parents are

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generally informed of such a diagnosis by first-line practitioners who are not familiar with AGD. This situation—at best nonoptimal and more often unfavorable—can be a source of great parental anxiety and distress. Further explanations and management by a multidisciplinary ADG team may not always compensate and make up for the initial flaws. This distress may lead to an inadequate request for pregnancy termination from the parents, depending on local regulations. It is highly debatable whether a severe AGD or a micropenis with potential sexual dysfunction is a "severe and untreatable defect" that may justify accepting the parent's request , as required by French law, for instance [1].

Parental curiosity and screening for sex-associated diseases remain the main reasons for determining fetal sex. But at present, prenatal screening for genital variants raises more questions and provides more difficulties than answers. It strongly challenges ethical principles in current medicine and adds uncertainty to the management of these fetuses and children in our fast-moving society.

Conflicts of interest: The authors have nothing to disclose.

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