Editorial

Wolfgang Holzgreve

Fetal anomalies – From prenatal diagnosis to therapy

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The term “fetal anomalies” would be better being replaced by the term “prenatal medicine”, because the medicine in the prenatal period strives for the same as any other specialty in medicine, which is providing in the case of an individual disease a precise diagnosis as the basis for an effective therapy. The specific difference is that in prenatal medicine the patient is not yet born, and therefore, for example, the 700 pages textbook on fetal therapy edited by two pediatric surgeons and two obstetricians has the title *The Unborn Patient* [1]. Unfortunately in some cases early diagnosis, e.g. of an anencephaly found by a first trimester ultrasound or of a severe inborn error of metabolism found by DNA investigation after chorionic villus biopsy, reveals an untreatable disease associated with the early death of the affected unborn patient, and then the expecting couple might even get into the difficult choice of carrying the pregnancy to term or having to consider as the ultimate option, the termination of pregnancy, causing the almost unsolvable conflict between the right to life for every human being and the autonomy of the pregnant woman who has to carry the dilemma. Fortunately, the chances for an effective therapy by proper prenatal diagnosis, perinatal management and postnatal care have increased dramatically over the last decades, e.g. in cases with blood group incompatibility or fetal heart disease [2]. Unfortunately, despite many efforts by professional organizations and charities, the clearly established approaches for an effective primary prevention of birth defects, e.g. by avoiding alcohol in pregnancy or using folate for the prevention of neural tube defects are not fully applied [3].

New genetic testing techniques as well as constant progress in the imaging technologies of the fetus have fundamentally changed the practice of prenatal diagnosis during the past decade [4]. The greatly improved non-invasive risk assessment for common fetal aneuploidies by recent cell-free DNA (cfDNA) testing technologies on maternal plasma [non-invasive prenatal testing (NIPT) or non-invasive prenatal screening (NIPS)] has been acclaimed by pregnant women and their doctors as

well and has resulted in a significant decline of invasive testing requiring chorionic villus sampling or amniocentesis. It has also provided a new insight into the fetal-maternal transfer of cells and cfDNA with major progress in understanding certain maternal immunologic diseases including preeclampsia [5]. A high sensitivity and low false-positive rate, in particular for trisomy 21 and to a lesser degree for trisomies 13 and 18, confirmed in a number of implementation studies, large series from single providers and collaborative studies have led to a steep increase in the number of NIPT cases [6, 7]. It took a while before attention was drawn to the positive predictive value (PPV) of NIPT, a parameter depending on the prevalence, i.e. pretest risk for a given aneuploidy and an important indicator of an individual false-positive test result. Grace et al. [8] now provide online calculators for an individual PPV in clinical practice and propose to include this with the lab report. Recent recommendations, e.g. by the American College of Medical Genetics and Genomics support this approach [9]. The predictive values are also a central issue in the discussion on the clinical utility of extended NIPTs encompassing sex chromosome anomalies, defined microdeletion syndromes or genome wide copy number variations (CNVs). Most commercial providers are offering some or all of these testing options already [10].

Despite the significant progress with NIPT this technique should not be offered in pregnancy care without a diagnostic ultrasound, and therefore the paper by Bardin et al. in this issue [11] on cytogenetic analysis in fetuses with abnormal sonographic findings is important, as well as the definition of the value of additional imaging modalities such as magnetic resonance tomography (MRT) by Van der Knoop et al. [12] or speckle tracking echocardiography by Rolf et al. also in this issue [13].

Prenatal diagnosis rests on a spectrum of modern techniques where typically a finding with one testing modality triggers an additional investigation, e.g. the sonographic finding of a non-immune hydrops fetalis leading to an invasive detection of an inborn error of metabolism (Bruwer et al. in this issue [14]).

Most of all in prenatal medicine we constantly have to critically re-evaluate our progress in diagnosis and therapy, e.g. to look at the neurologic complications after 24 months following therapy for fetal-fetal transfusion syndrome in twins *in utero* (Miralles-Gutierrez et al. in this issue [15]), and the principles of evidence-based medicine have always to be applied.

Prenatal medicine, which has the fetus as the patient, is a fascinating field because of the amazing progress over the years coming directly from major advances in imaging and genetic techniques, but it should constantly be embedded in professional counseling that perinatologists must always consider the ethical implications of the sometimes very difficult decisions. Our primary duty in prenatal medicine as well as in the society in general is to care for handicapped people including those with congenital anomalies in the best possible way, and the offer of prenatal diagnosis burdens the providers with enormous responsibility. The clearly defined goal is to use the ever improving diagnostic tools for implementing more effective therapies in time- and that is what prenatal medicine is all about.

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Wolfgang Holzgreve, MD, FRCOG, FACOG, MBA, Professor of Obstetrics and Gynecology, Medical Director and CEO, University Medical Center Bonn, Sigmund-Freud-Strasse 25, 53105 Bonn, Germany, Tel.: +49 228.287-10900, Fax: +49 228.287-90 10900, Mobile: +49 151.58 233 667, E-mail: wolfgang.holzgreve@ukbonn.de, wolfgang@holzgreve.net