Introduction

Prenatal screening for congenital anomalies, using ultrasound techniques for the so called *structural anomaly scan,* is traditionally performed in the second trimester of pregnancy. Ultrasound is, as a non-invasive technique, of course preferred above exposure to ionising radiation. The technique improved significantly the last decades as well as the availability, both resulting in a broad clinical experience with this technique. Importantly, when the so-called *as low as reasonably practicable* (ALARP) principle is respected, ultrasound is generally regarded as a safe diagnostic instrument for both mother and child.[1]

Detecting congenital anomalies

Although the structural anomaly scan usually is scheduled in the second trimester of pregnancy, there is an increasing interest in the detection of structural abnormalities in the first trimester.[2-4] Nuchal translucency measurement - as part of the combined test - and technical improvement of ultrasound equipment, yielding an improved visualisation, have contributed to this shift of interest from the second to the first trimester. Early detection of abnormalities has great advantages compared to detection later in pregnancy. For instance, early prenatal diagnosis of congenital anomalies provides more time for physicians to counsel and more time for the patients to consider all treatment options, including termination of pregnancy.[5] There are however drawbacks, mainly caused by marked changing anatomy in the first trimester of pregnancy. To be able to diagnose abnormal development, a profound knowledge of the transforming anatomy of the developing human embryo is necessary. Although additional testing may enhance the detection rate of congenital anomalies and early prenatal screening may increase sensitivity, specificity may concurrently be decreased.[6] Therefore, familiarity with the specific sonographic appearance of normal development in early pregnancy is utmost important for optimising these test characteristics.

Third dimension

In daily obstetric practice, two-dimensional (2D) ultrasound is used to screen for and to diagnose congenital anomalies. 3D imaging has however multiple advantages over conventional 2D ultrasound. By obtaining a 3D volume instead of a 2D plane, very precise localisation of structures can be achieved via the orthogonal triplanar image, which can help in confirming diagnoses.[7] Furthermore, surface-rendered 3D volumes provide the possibility to evaluate surface abnormalities and may aid in counselling future parents.[8, 9] By using special software, like Virtual Organ Computer-aided AnaLysis (VOCAL™; GE Medical Systems, Zipf, Austria) it is even possible to add the third dimension on a two-dimensional (2D) screen creating the opportunity to measure volumes.[10]

3D virtual reality

Recent developments in 3D techniques have resulted in improved imaging. A new visualisation approach allows 3D volumes to be translated into a Cartesian format to be displayed in a Cartesian coordinate system, like the BARCO I-Space (Barco N.V., Kortrijk, Belgium). The BARCO I-Space is based on a 3D virtual reality (VR) environment that allows depth perception and interaction with the ultrasound data in a more natural and intuitive way compared to 3D images displayed on a 2D screen. This 3D VR technique has already proved its value in obstetric ultrasonography, e.g., the determination of ambiguous genitalia in a later stage of pregnancy[11] and the evaluation of conjoined twins.[12] Also in a preclinical setting, 3D VR has given ample insight in the early development of extra-embryonal structures like the trophoblast/placenta[13, 14] and the umbilical cord, vitelline duct and yolk sac.[15] This technique additionally provides the possibility to obtain volume measurements being different in normal pregnancy[16, 17] and in aneuploid pregnancies[18] and therefore seems to be a promising innovation in prenatal diagnosis.

Aims and outline of this thesis

The general aim of research of this thesis was to better understand normal physiological changes of the developing human embryo by using novel imaging techniques, serving as a background for determining the difference between normal and abnormal development. We examined the sonographic appearance of the brain, midgut, genitalia, feet and the curvature in the first trimester of pregnancy by means of both 3D and 3D VR technology.

The following research objectives were defined:

1. To describe first trimester growth trajectories of the telecephalon, diencephalon and mesencephalon using 3D ultrasound. Compared to other organ systems, relatively little is known about cerebral development in utero.
2. To investigate the development of the physiological exomphalos using 3D VR. During normal development of the midgut in the first trimester, the intestines protrude into the umbilical cord causing an omphalocoele. Pathological omphalocoele is generally regarded as a major congenital anomaly and might be caused by its physiological counterpart failing to resolve.
3. To evaluate the development of the lower leg and foot during the period of transient ‘physiological clubfoot’ using 3D VR. A clubfoot (pes equinovarus) is a congenital anomaly with a relatively high incidence.
4. To investigate whether there is scientific basis for reliable sex determination at the end of the first trimester of pregnancy using 3D VR being the best available technique for studying embryonic surface development. Although the foetal genitalia have not been developed entirely at the end of the first trimester of pregnancy, several clinicians and authors report to be able to predict the sex of the baby at that moment.
5. To describe, for the first time, the development of the embryonic curvature using 3D ultrasound. Additionally we investigated whether embryos from pregnancies resulting in a miscarriage have differences in the curvature compared to ongoing pregnancies.

The implications and limitations of this research, but also new opportunities, are discussed at the end of the thesis.

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