General discussion

The studies in this thesis present ultrasonographic evaluation and documentation of various physiological changes during early human development, being necessary for appropriate first trimester diagnostic procedures. Detailed knowledge on normal anatomy and physiology is essential to recognise pathology. In this thesis some morphological changes during organogenesis are studied. The developing organ systems studied were selected because of questions raised during clinical first trimester two-dimensional (2D) and three-dimensional (3D) ultrasound. These specific questions are described in the research objectives defined in the introduction to this thesis. The answers to these questions, although not all of them immediately applicable for clinical purposes, may serve as a background for attempts to improve first trimester detection of congenital anomalies in the near future.

Early diagnosis

The trend towards early sonographic screening for detection and diagnosis of structural anomalies is in line with other trends in obstetrics and prenatal diagnosis. For instance, the detection of cell free foetal deoxyribonucleic acid (DNA) in maternal blood provides the possibility of non-invasive diagnosis of chromosomal abnormalities at an early gestational age. First trimester biomarkers and uterine artery Doppler measurements are used to determine the risk of placental disorders like foetal growth restriction and pre-eclampsia later on in pregnancy. Early diagnosis and risk assessment offers physicians more time for counselling or to run additional confirmatory tests. In case of a congenital anomaly more time will become available for patients to take all treatment options into consideration, including termination of pregnancy. This is especially important in countries having gestational age related legal restrictions for termination of pregnancy, to avoid extrajudicial abortion.

There is another important, potentially beneficial, aspect of prenatal examination in the first trimester. Ultrasonographic visualisation improves significantly by using high frequency vaginal ultrasound probes as compared to low frequency abdominal probes, used in the second trimester. With vaginal ultrasound there is less interference of fat tissue and therefore less

absorption of ultrasound. However high frequency, resulting in high resolution, is associated with a decreased penetration of ultrasound resulting in a smaller scanning area. Vaginal ultrasound is therefore only suitable for first trimester ultrasound and not for routine second trimester ultrasound. A shorter duration of the investigation time, as a result of improved image quality, and an intensity reduction of the ultrasound energy, as a result of a shorter distance between the transducer and the embryo, both contribute to a reduced exposure time. Off-line examination of 3D and 3D virtual reality (3D VR) images furthermore reduces the exposure time and contribute to a safer procedure. It should be noted, though, that as long as low-intensity imaging is used and examiners adhere to the aforementioned ALARP-rule there is no scientific proof that sonography could be harmful in early pregnancy. The same applies to 3D ultrasound.[1]

There is a potential danger that the details observed during vaginal ultrasound by the clinician are not always understood and may lead to misinterpretation of normal morphology during normal embryonic development. This consideration necessitates more studies like the ones described in this thesis: research concerning normal foetal development during the first trimester.

Improving test characteristics

Increasing knowledge on first trimester ultrasound appearance of first trimester embryonic structures will improve the test characteristics by reducing the number of false positive and false negative findings. Our data may help in the prevention of both false positive and negative diagnoses in early pregnancy.

Relatively little is known about precise ultrasonographic details of first trimester brain development. We created size charts of the walls of the telencephalon, diencephalon and mesencephalon, which may help in diagnosing abnormal development of the central nervous system already in a very early stage of pregnancy (chapter 2).

Knowing the normal appearance and seize of a physiological omphalocoele (chapter 3) is very helpful in avoiding the wrong diagnosis of a pathological first trimester exomphalos. Using 3D VR we are the first to add the third dimension, yielding size charts of the volume of the omphalocoele as well.

The exact mechanism causing congenital clubfeet is still unknown. We confirmed in vivo a transient clubfoot stage in the development of the lower limb at 10-11 weeks gestational age (chapter 4). Our data may support further research on the aetiology of this relatively common anomaly.

The determination of the foetal sex in an early stage of pregnancy may be important in inheritable diseases. We showed that the determination of foetal sex should not be performed sonographically in the first trimester. An accurate determination turned out to be not possible by both quantitative and qualitative means (chapter 5). Amplification of cell-free foetal DNA in maternal blood, however, is, although expensive, an excellent and almost 100% accurate alternative.

Embryonic curvature is inversely correlated with gestational age. We introduced a measurement for this characteristic of growth and development and created reference charts (chapter 6). These charts may help in research on neural tube defects and other spinal abnormalities, in which embryonic curvature might be compromised.

Precautions

There are nevertheless potential downsides to these new insights. Routine ultrasound in early pregnancy will not only reveal more anomalies but also at an earlier gestational age. Some of these pregnancies would have ended in a miscarriage anyway. This overdiagnosis may cause more anxiety in pregnant women.[2] On the other hand, these formerly unknown diagnoses could provide an opportunity for genetic testing and may help in preconception counselling for future pregnancies.

We should also be aware of the fact that every examination bears the risk of a false-positive diagnosis. Extra testing will probably yield more false-positive findings. Even in case subsequent sonography appears to be normal, distress in future parents has already been initiated. It is therefore necessary that future parents are thoroughly counselled beforehand about the possibility of false-positive findings.[2]

Future

Although the new techniques have been proven to be useful, especially during the first trimester, conventional 2D imaging cannot just be replaced right now by 3D and 3D VR ultrasound. These new techniques, however, are already a useful help in diagnosis and counselling.

While 3D ultrasound is omnipresent in specialised centres for prenatal diagnosis, the possibility of performing 3D VR is not. We developed a desktop version of the BARCO I-Space with comparable VR imaging, using polarising glasses and a joystick, including the same 3D VR measurement tools.[3] We expect that with this simplified technical improvement, also resulting in a substantial reduction of acquisition costs, the 3D VR technique will become available as a built-in application in ultrasound equipment in the near future.

For some congenital anomalies, routinely detected in the second trimester, the question remains whether these can be detected in an earlier stage. Future research is necessary to find a reliable answer to this question for much more anomalies than studied in this thesis. For this type of research routinely stored first trimester 3D volumes are utmost important for creating the opportunity for looking back to observe if the particular abnormality was already present in the first trimester or not. Also, since most anomalies are nowadays diagnosed in the second trimester by means of 2D ultrasound, the cost and time efficiency of 3D imaging and of first trimester sonography has yet to be determined.

Conclusion

3D sonography and 3D VR enable us to gain new insights in physiological early human development and may improve diagnostics. If used prudentially, these techniques will probably show its many benefits in future.

References

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