Renal Function and Urine Production in the Compromised Fetus

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1. Introduction

Fetal urine production begins in the first trimester. Autopsy findings of filled urinary bladders in human fetuses have been reported from 11 gestational weeks (Abramovich, 1968). In 1970, the first report on ultrasound investigations of the fetal urinary bladder was published (Garrett et al., 1970). Three years later, a method for estimating fetal urine production was introduced (Campbell et al., 1973).

In this paper, a short summary of amniotic fluid turnover is presented. Moreover, fetal renal development, artery flow velocity and urine production in normal and compromised fetuses are dealt with. The gradual development of the 2D ultrasound technique for estimating of the fetal urine production rate (HFUPR) is described. In addition, some confounding factors are mentioned. Finally, two important clinical questions, which must be taken into consideration when utilising the HFUPR for fetal surveillance, are identified.
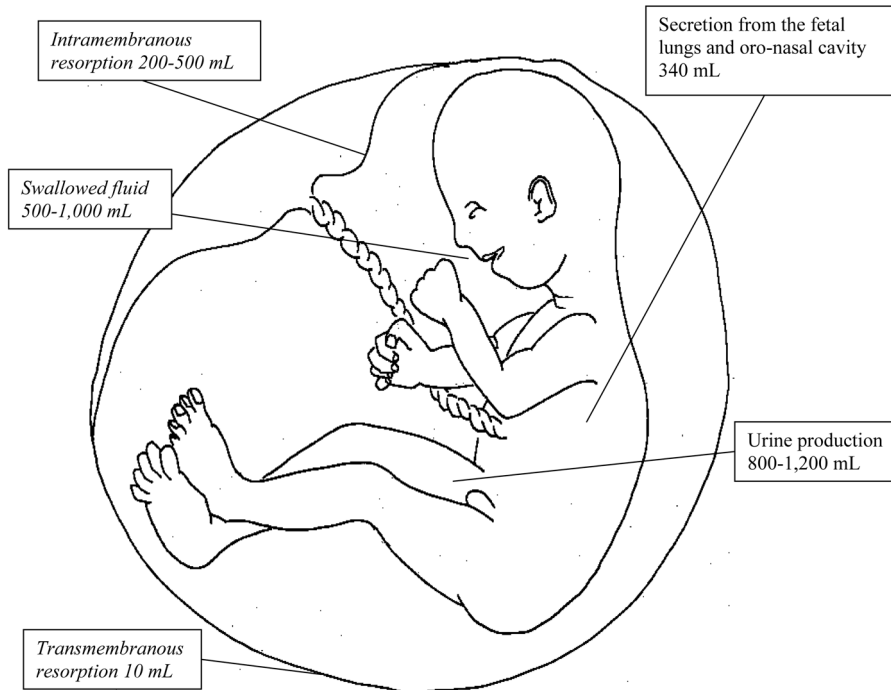
2. Amniotic fluid

The volume of amniotic fluid increases during pregnancy (Queenan et al., 1972). In general, the secretion of liquid by the kidneys and from the fetal lungs and oro-nasal cavity is balanced by the removal of equal amounts of liquid (Flack et al., 1995). The main clearance pathway is the swallowing of fluid by the fetus. Additionally, albeit to a lesser degree, fluid passes from the amniotic lumen via the surfaces of the placenta and umbilical cord into the fetal blood circulation (the intramembranous pathway) and into the mother's circulation (the transmembranous pathway) via the uterine wall through the surface of the amniotic sac outside the placental border.

2.1 Abnormal amounts of amniotic fluid

Oligohydramnios (reduced volume < 300 mL) is found in 3-5% (Hansmann, 1985; Volante et al., 2004). Rupture of the membranes is the most common cause of oligohydramnios. A reduction in amniotic fluid volume is of particular concern when it occurs in conjunction with structural fetal anomalies, fetal growth restriction, kidney abnormalities, postdate pregnancies and maternal disease. In these high-risk conditions, it is associated with a poor perinatal outcome (Camanni et al., 2009; Hill et al., 1983). Early onset of oligohydramnios

adversely affects fetal lung development, resulting in pulmonary hypoplasia, which might lead to death from severe respiratory insufficiency (Nicolini et al., 1989). However, numerous factors complicate the ultrasonographic diagnosis of oligohydramnios. They include the lack of a complete and detailed understanding of the physiology of the dynamics of oligohydramnios. For example, in 40%, the oligohydramnios occurs without any high-risk conditions and the current available data support the expectant non-interventional management of these cases complicated by isolated oligohydramnios (Sherer, 2002).

Data: Gilbert WM och Brace RA. Amniotic fluid volume and normal flows to and from the amniotic cavity. Semin Perinatol. 1993; 17: 150-157

Fig. 1. The amniotic fluid turnover at term. Half the secreted liquid from the fetal lungs and oro-nasal cavity reaches the amniotic sack and the other half is swallowed. The clearance pathways are denoted in italics.

Polyhydramnios (increased volume > 2,000 mL) is found in 1-3% (Volante et al., 2004). The underlying cause of excessive amniotic fluid volume is obvious in some clinical conditions in some clinical conditions and in cases of an minor an minor increase in amniotic fluid volume, the perinatal outcome is good. However, maternal kidney disease, diabetes type 2 and fetal conditions, such as chromosomal abnormalities, most commonly trisomy 21, followed by trisomy 18 and trisomy 13, might be causes (Hill et al., 1987). Moreover, polyhydramnios can be the result of oesophageal atresia and defects in the fetal CNS (Barkin et al., 1987; Kimble et al., 1998).

In cases with abnormal amniotic fluid volume, prenatal ultrasonography has been recommended for the evaluation of fetal anatomy and growth, swallowing patterns, blood flow velocity in different vessels and repeated estimation of the amount of fluid.

3. Fetal urine production

During the filling phase, the increasing volume of the urinary bladder can be observed, documented and assessed by ultrasound scans.
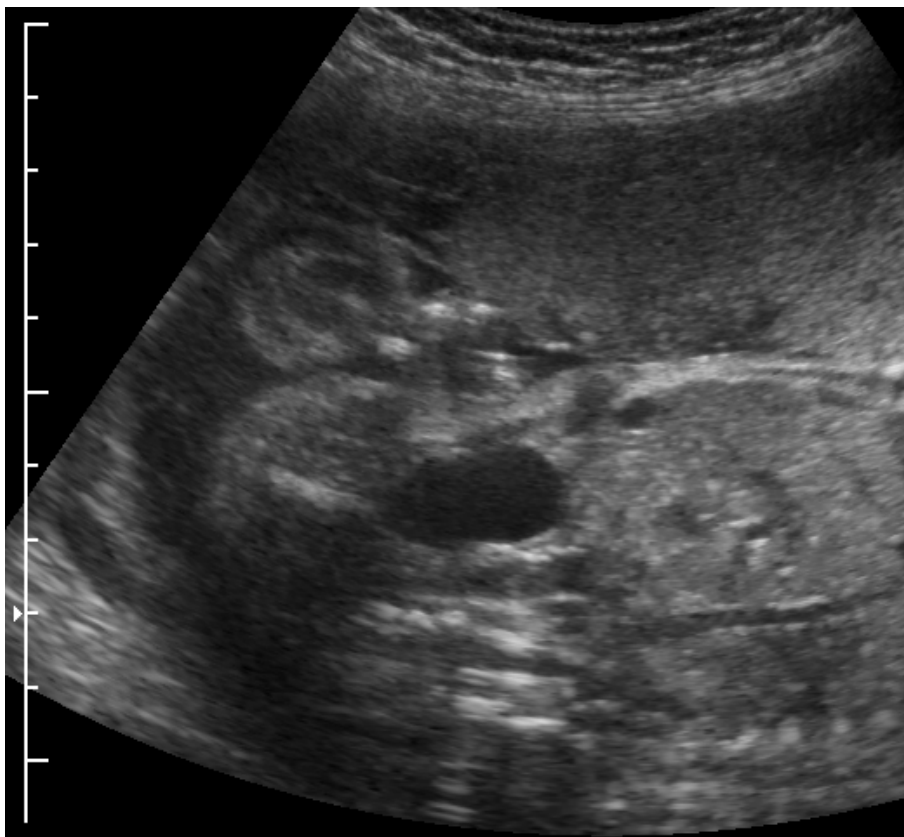
Fig. 2. This figure shows an appropriate longitudinal bladder image. The 2D ultrasound image on the ultrasound screen was documented on a CD and the volume was calculated in a computer.

The Hourly Fetal Urine Production Rate (HFUPR) can be estimated by regression analysis of calculated bladder volumes documented at different time points within one filling phase (Campbell et al., 1973; Fagerquist et al., 2001; Groome et al., 1991; Nicolaides et al., 1990; Rabinowitz et al., 1989; van Otterlo et al., 1977; Wladimiroff and Campbell, 1974), or by the difference between the maximum and minimum volumes divided by the time interval (Deutinger et al., 1987; Shin et al., 1987; Takeuchi et al., 1994).
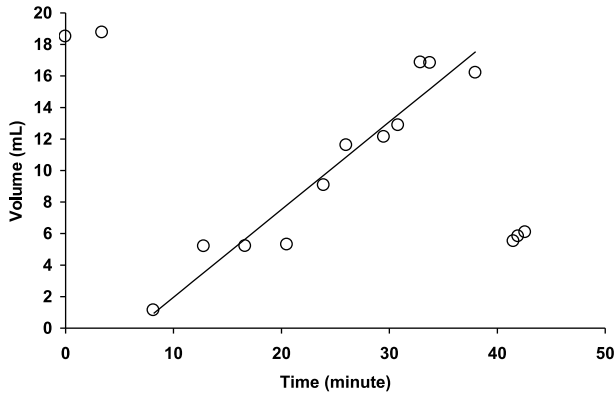
Fig. 3. The Hourly Fetal Urine Production Rate (HFUPR) estimation was based on the increase in bladder volume during a filling phase and extrapolated to a time span of one hour.

The filling and emptying dynamics of the fetal urinary bladder have been investigated in detail. The mean time for the bladder-filling phase was 25 minutes (range 7-43 minutes) and it was not significantly influenced by gestational age (Rabinowitz et al., 1989).

Gestational age (weeks)	Maximum volumes (mL)	HFUPR (mL/hour)
20	1	5
21	2	6
22	2	7
23	3	8
24	4	9
25	5	10
26	6	11
27	7	13
28	9	14
29	10	16
30	11	18
31	13	20
32	14	22
33	16	25
34	18	27
35	20	30
36	22	33
37	24	37
38	27	41
39	30	46
40	32	51

(Rabinowitz R, Peters MT, Vyas S, Campbell S, Nicolaides KH. Measurement of fetal urine production in normal pregnancy by real-time ultrasonography. Am J Obstet Gynecol 1989;161(5):1264-6)

Table 1. The maximum bladder volumes before emptying and HFUPR at different gestational ages were calculated by the author according to formulas in the reference article.

3.1 Urine production in the intra-uterine growth-restricted fetus

When comparing Intra-Uterine Growth-Restricted (IUGR) fetuses with Appropriate weight for Gestational Age (AGA) fetuses at the same gestational age, the HFUPR was significantly lower for IUGR fetuses (Nicolaides et al., 1990; Takeuchi et al., 1994; van Otterlo et al., 1977; Wladimiroff and Campbell, 1974). However, there were no significant differences when the IUGR fetuses were compared with controls of corresponding body weights but with lower gestational ages (Wladimiroff and Campbell, 1974). It was assumed that the reduced urine production rate for IUGR fetuses reflected renal hypoplasia, due to growth retardation. Although different investigations have presented various normal values, the HFUPR in IUGR fetuses compared with fetuses of normal size (AGA) has generally been reported to be lower (Nicolaides et al., 1990; Takeuchi et al., 1994; van Otterlo et al., 1977).

4. Fetal kidneys

In a human 2D ultrasound study comprising IUGR and AGA fetuses, the volume of fetal kidneys, as well as the urine production rate, was estimated (Deutinger et al., 1987). In IUGR fetuses, both the volume of the kidneys and the HFUPR were significantly reduced when compared with the AGA fetuses. In agreement with this study, the growth of fetal kidneys was significantly slower in Small for Gestational Age (SGA) vs. AGA fetuses when it came to the anterio-posterior diameter and transverse circumference of the kidneys (Konje et al., 1997). This divergence was most marked after 26 weeks of gestation.

The fetal kidneys gradually increase in volume with gestational age (Hansmann, 1985). Renal weight as an autopsy finding is, however, often compromised and associated with a coefficient of variation as large as 50%, due to oedema and passive venous engorgement. Renal functional capacity depends on the number of nephrons, but no known relationship exists between renal weight and the number of glomeruli (Hinchliffe et al., 1991). For many years, estimates of glomerular numbers have therefore been derived using a variety of methods (Bendtsen and Nyengaard, 1989). Unfortunately, these methods have been shown to have some degrees of bias. However, a new stereological dissector technique permits the direct, unbiased estimation of glomerular numbers (Hinchliffe et al., 1992). This new dissector method was used to estimate the number of nephrons in fetuses. The number was 15,000 per kidney in human fetuses at 15 gestational weeks and between 740,000 and 1,060,000 at term.

The total number of nephrons was estimated in a comparative investigation of six IUGR stillbirths of known gestational age with controls comprising eleven stillbirths with a birth weight greater than the 10th percentile (prenatal period) and eight liveborn IUGR infants, who died within a year of birth, with a control group of seven appropriately grown infants who also died within a year of birth (postnatal period). The number of nephrons for five of the six IUGR stillborn children and all the growth-retarded children who died within one year was significantly reduced compared with the controls (Hinchliffe et al., 1992). Moreover, in animal models, growth restriction has been associated with a reduced number of nephrons (Bauer et al., 2002; Bauer et al., 2003). It has been suggested that the mechanism underlying the reduced number of nephrons in IUGR fetuses is increased apoptosis due to changes in the levels of apoptosis-related proteins (Pham et al., 2003).

4.1 Renal artery flow velocity and urine production in fetuses with hypoxemia

The HFUPR was determined by 2D ultrasound immediately before cordocentesis for blood gas analysis in 27 Small for Gestational Age (SGA) and 101 AGA fetuses (Nicolaides et al., 1990). The HFUPR was reduced in the group of SGA fetuses in comparison with AGA fetuses. Furthermore, the reduction in urine production for the SGA fetuses was correlated with the degree of fetal hypoxemia, while the degree of fetal hypoxemia did not correlate with the degree of fetal smallness.

Several studies demonstrate associations between increased impedance in the fetal renal arteries and factors suggestive of compromised fetal conditions and, in some studies, also reduced urine production rates (Mikovic et al., 2003; Miura, 1991; Stigter et al., 2001; Vyas et al., 1989). In one study, the renal artery flow-velocity wave forms were examined in normal and hypoxemic human fetuses (Vyas et al., 1989). The Pulsatility Index (PI), which is peak systolic velocity minus end diastolic velocity over mean velocity, was higher in SGA than in AGA fetuses. Furthermore, using cordocentesis in the SGA fetuses, a significant, direct correlation was found between blood oxygen deficit and increased renal artery PI (Vyas et al., 1989). Moreover, in a study of 35 IUGR fetuses, the PI in the fetal renal arteries was significantly increased (Mikovic et al., 2003). In studies of fetal urine production, it was demonstrated that the PI in the renal artery was higher in IUGR than in AGA fetuses and that it displayed a negative correlation with the urine production rate and the amniotic fluid volume (Miura, 1991). In spite of varying results regarding the PI in fetal renal arteries (Silver et al., 2003; Stigter et al., 2001), the data suggest that, in fetal hypoxemia, there is a redistribution of blood flow, with a decrease in renal blood perfusion and a decrease in HFUPR. These findings may be important, as it would be of great clinical interest to detect whether or not a particular fetus with growth restriction is further compromised.

5. Confounding factors

A highly significant diurnal rhythm was observed in an on-line, computerised study of sheep (Brace and Moore, 1991). In that study, the urine flow rate was measured continuously over a period of days. In 8/9 animals, the peak flow rate occurred at around 9 pm, while it occurred at 9.30 am in the remaining sheep fetus. The maximum urine flow was 28 ± 5% above the 24-hour mean. Although this significant diurnal variation was demonstrated in an animal model, it is important not to disregard a possible diurnal variation in human fetal urine production as well.

The urine production rate was estimated two hours before and two hours after maternal breakfast in 25 AGA and 15 IUGR fetuses. After breakfast, the HFUPR increased in AGA fetuses but did not change in IUGR fetuses (Yasuhi et al., 1996). The PI of the fetal renal artery was significantly reduced after maternal food ingestion in uncomplicated pregnancies (Yasuhi et al., 1997). To our knowledge, no conflicting reports have been published and, to avoid the confounding variation due to diurnal variation and maternal meal ingestion, it is recommended that the estimation of fetal urine production should be performed under standardised conditions. Also, maternal water ingestion might influence the fetal urine production rate (Flack et al., 1995; Oosterhof et al., 2000).

6. Methods for estimating the volume of the fetal urinary bladder

Calculated bladder volumes cannot be validated in living human fetuses, as the true fetal urinary bladder volumes are not known. The reliability of the estimated bladder dimensions, on the other hand, has been evaluated using the 2D ultrasound technique (Fagerquist et al., 2001; Fagerquist et al., 2003; Fagerquist et al., 2002). The calculation of the measurement error was based on the variability in repeated estimations of identical bladder volumes. Standard deviation (SD) was used because the variation was normally distributed. Furthermore, there was a linear relationship between bladder volume and the measurement error, which has been thoroughly documented in three previous studies (Fagerquist et al., 2001; Fagerquist et al., 2003; Fagerquist et al., 2002). This is a prerequisite for using a linear regression function (Skrepnek, 2005).
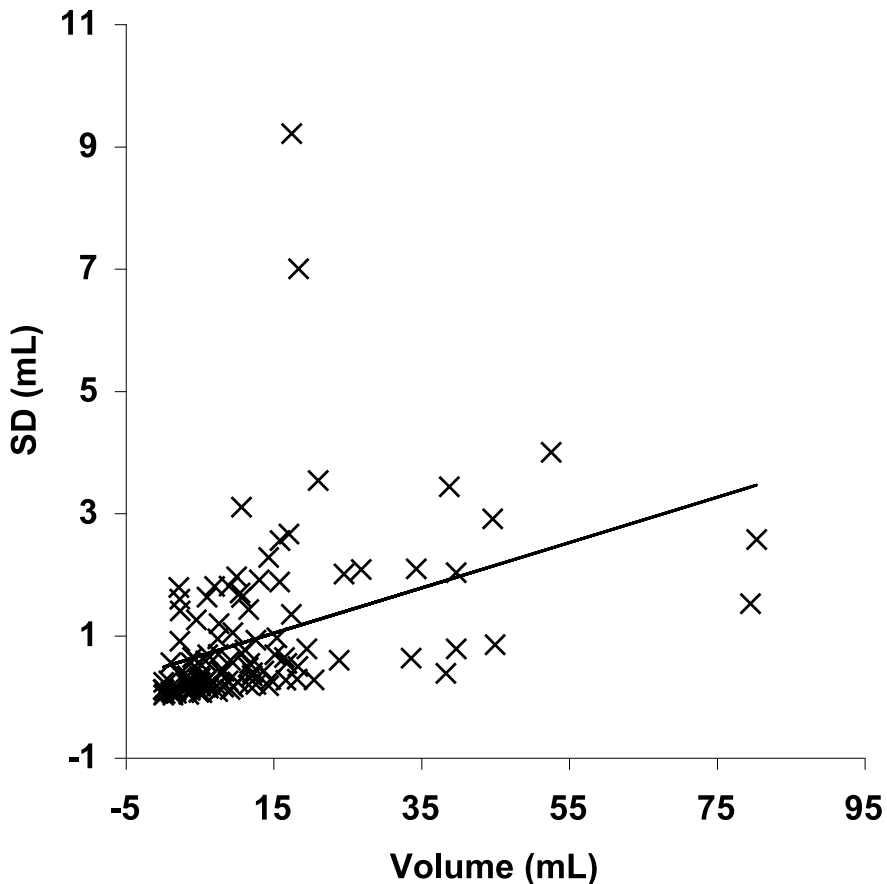

Fig. 4. The SD was calculated when estimating the bladder volume of 120 fetuses. Different methods were used and this gave rise to 222 relationships between SD and bladder volume. The maximum and minimum bladder volumes were 80.5 mL and 0.1 mL respectively. The distribution of the SDs supports a linear relationship (correlation coefficient 0.36).
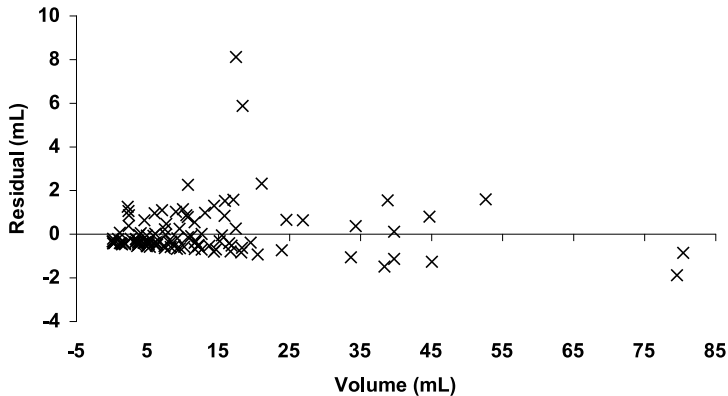
Fig. 5. The distribution of the residuals supports a linear relationship between the SD and bladder volume based on 222 relationships between the SD and bladder volume. The maximum and minimum of the residuals were 8.2 mL and -1.9 mL respectively. The mean was 0.00 mL and the median -0.37 mL.

One important finding was that the fetal urinary bladder can be regarded as a rotational body. This means that an appropriate 2D longitudinal image of the fetal bladder has all the information that is needed for volume calculation. This discovery simplifies the way the volume can be calculated.

The method for estimating the volume of the fetal urinary bladder was gradually developed in order to reduce the SD for volume estimation. In the first paper, the volume measurement errors (SD) when using the conventional method and the ellipsoid formula were analysed (Fagerquist et al., 2001). The SD for the measurement error was 17.3-10.9% for bladder volumes of 5-40 mL.

By introducing the sum-of-cylinders method, the SD was significantly reduced to 8.8-3.5% (p=0.0032) (Fagerquist et al., 2003).

6.1 The 2D technique and the sum-of-cylinders method

Before volume computation, the operator performed an interactive process using the Microsoft-Paint and Microsoft Excel computer programs. The bladder image documented in the Microsoft-Paint format and the data of calibration in an Excel sheet were activated in the MathCad computer program.
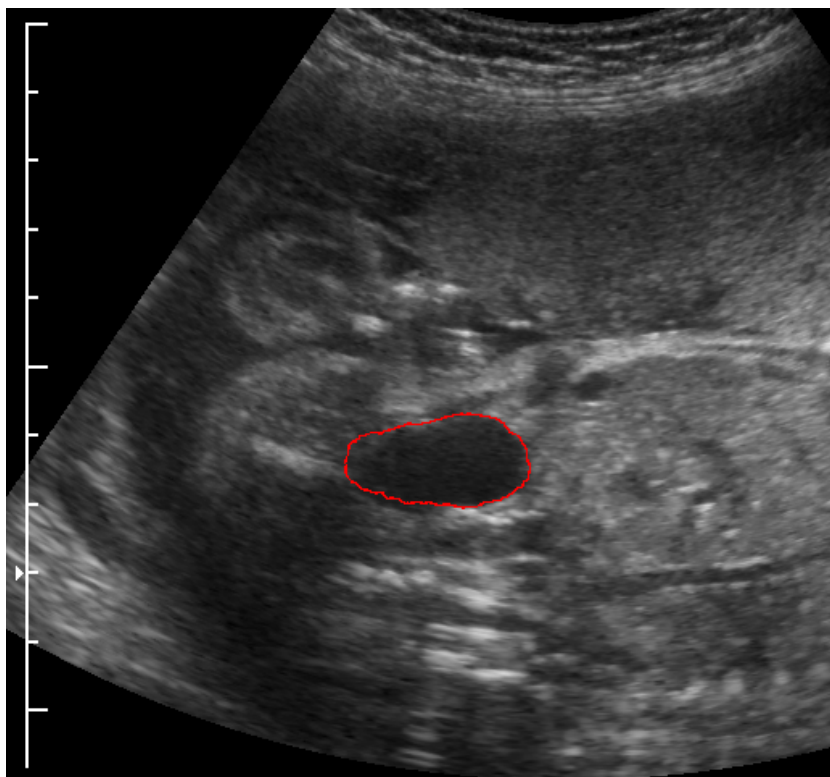
Fig. 6. The image that was going to be used for volume computation according to the sum-of-cylinders method was created in an interactive process. Firstly, the operator traced the bladder borders with a red digital marker on the computer screen using the Microsoft-Paint computer program.

The software determines the co-ordinates for the bladder boundary pixels. The image was analysed by the software and each column of pixels was scanned 1) from left to right on the screen, moving from top of the image to bottom in each column to identify the red marked top pixel of the bladder border and 2) from right to left on the screen, moving from bottom of the image to top in each column to identify the red marked bottom pixel of the bladder border. The length of each vertical strip (from top to bottom red pixels in each column) perpendicular to the long axis was computed. The length of each strip was regarded as the diameter of a cylinder, one pixel high. The total bladder volume was calculated by adding all the cylinders.

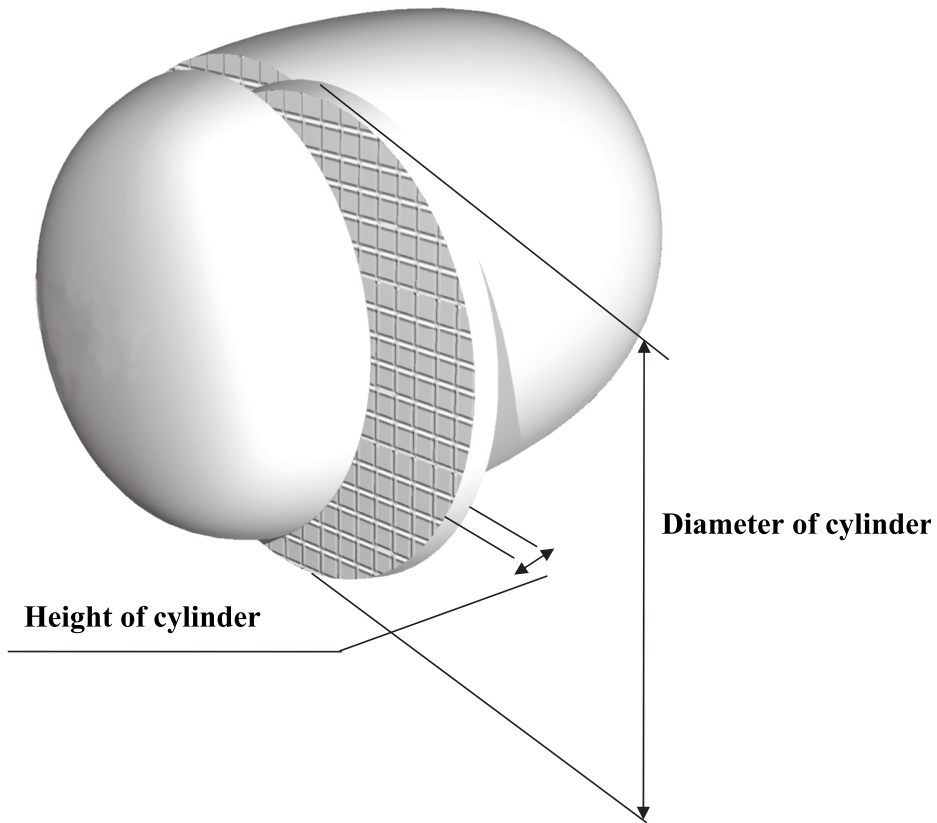**Diameter of cylinder**

Height of cylinder

Fig. 7. Using the MathCad computer programs, the vertical distances between marked pixels included in the bladder border was estimated. The bladder image was then electronically subdivided in vertical cylinders and the sum of these cylinders with the height of one pixel equals the bladder volume.

6.2 The 3D ultrasound technique

The 3D ultrasound technique and integrated software, such as the "Virtual Organ Computer-aided AnaLysis" system (VOCAL™), are already available for volume estimation and measurements in the in vitro setting and are both reliable and valid (Raine-Fenning et al., 2003). Moreover, this technique has been applied to the fetal urinary bladder (Lee et al., 2007; Touboul et al., 2008). Unfortunately, the 3D technique is prone to the same types of problem encountered in 2D ultrasound imaging, plus others unique to volume acquisition and visualisation (Nelson et al., 2000). When selecting the initial bladder image, the operator can avoid shadows from the fetal pelvis. However, according to the VOCAL system, the subsequent process for volume estimation is automatic and disturbing shadows are not avoided. Furthermore, in this program, only 40 electronic points are available for the contour marking, which is another disadvantage.

On the other hand, when using the 2D ultrasound technique, the operator can avoid disturbing shadows by selecting an appropriate longitudinal bladder image. The bladder is defined by the operator who electronically marks the pixels, which are included in the bladder contour. Typically, this corresponds to 200-300 pixels in the boundary. In this way, the technical limit for optimal precision, one pixel, is reached; this is the smallest unit of display resolution.

7. The measurement error when estimating the HFUPR

When estimating the HFUPR, the measurement error is made when assessing the volume of the bladder, and that SD has been estimated for the 2D technique and the sum-of-cylinders method. There are some other factors that influence the HFUPR measurement error, the magnitude of the HFUPR and the number and time points of bladder image capture. To date, no information relating to the SD for bladder volume estimation by 3D ultrasound, which is a prerequisite for the subsequent analysis of estimation accuracy, is available.

When utilising the HFUPR for fetal surveillance, it is necessary to know whether the estimated HUFPR is pathologically low, i.e. below the 5th percentile point. It is therefore necessary to answer the question: 1) What is the risk of false readings at the 5th percentile point, for example, even though the true HFUPR is at a higher percentile point? Furthermore, it is necessary to answer the question: 2) How much of an observed HFUPR change (for example, during daily controls) can be explained exclusively by measurement error? The implication of the volume measurement error was demonstrated in detail in a publication publication concerning the 2D technique and the sum-of-cylinders method. (Fagerquist et al., 2010).

8. Conclusion

The data suggest that, in fetal hypoxemia, there might be a redistribution of blood flow, with a reduction in both renal perfusion and fetal urine production rate, which can be estimated by ultrasound. These findings may be important, as it would be of great clinical interest to determine whether or not a particular fetus with growth restriction is further compromised. To utilise the HFUPR, for fetal surveillance, a program is available for estimating the risk of false readings at a low percentile point, even though the true HFUPR is at a higher percentile point, and the degree to which an observed HFUPR change can be explained exclusively by measurement error.

9. Acknowledgments

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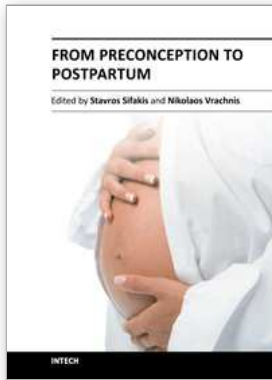
From Preconception to Postpartum

Edited by Dr. Stavros Sifakis

Obstetrics is evolving rapidly and finds itself today at the forefront of numerous developments. Providing selected updates on contemporary issues of basic research and clinical practice, as well as dealing with preconception, pregnancy, labor and postpartum, the present book guides the reader through the tough and complex decisions in the clinical management. Furthermore, it deepens the scientific understanding in the pathogenetic mechanisms implicated in pregnancy and motivates further research by providing evidence of the current knowledge and future perspectives in this field. Written by an international panel of distinguished authors who have produced stimulating articles, the multidisciplinary readers will find this book a valuable tool in the understanding of the maternal, placental and fetal interactions which are crucial for a successful pregnancy outcome.

How to reference

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