4. DISCUSSION

4.1 Definition of "Risk Pregnancies"

One of the major problems in understanding whether DSUA is helpful in low-risk pregnancies is the lack of a clear definition of "low-risk" and "high-risk". Even the term "medium-risk" is in use [17,56]. Using the "well-defined" German system is not very helpful, since the definition containing 26 topics concerning patients' history and 26 topics relating to the present situation is so extensive and non-specific that the major part of pregnancies would fulfil the criteria of "high-risk" pregnancy. On the other hand, it is clear that a system regarding mainly anamnestic data of previous pregnancies of the same patient [75] misses most of the relevant complications in primiparous women. There is evidence that especially in primigravidas DSUA seems to be helpful [5,29].

With a registered incidence of 0.68% of pre-eclampsia, 0.35% of placental abruptio, 3.89% of fetuses below the 10^{th} centile according to the normal values of Yudkin [74] and a perinatal mortality rate of 0.27% (Table 1), the present study group fulfilled the criteria of a low-risk group, at least with regard to pregnancy outcome. The study did not consider specific risk factors like placental position, which is well known to influence uterine artery waveform and pregnancy outcome [8,41,42,43] for two reasons:

- on the one hand, the description of laterality of placenta position seems to be rather arbitrary [16]
- on the other hand, an asymmetrical placental position will lead to an elevation of the impedance of the non-placental artery and, consequently, an increase in the mean impedance of both sides. This is registered by the "combination methods"

Also, the study did not regard other aspects like elevated maternal serum AFP, antiphospholipid syndrome or hemostatic abnormalities which are well known risk factors for adverse pregnancy outcome [19,44,71], since the purpose was to investigate the predictive power of DSUA independent of other factors. Neither did

the study regard smoking which is reported to be correlated with a higher incidence of placental abruption [4] and a reduced risk of pre-eclampsia [21].

4.2 Problems of Evaluation

Table 14 gives an overview of 16 studies which evaluate the diagnostic potential of DSUA in “low risk pregnancies”. They yielded controversial results mainly due to methodological differences concerning

- time of assessment
- definition and registration of outcome variables
- therapeutic interventions
- definition of abnormal waveform

4.2.1 Time of Assessment

The time of assessment seems to have a major impact on sensitivity and specificity of the method in predicting pregnancy complications. Based on the assumption that subsequent problems result from problems in trophoblastic invasion in early pregnancy practitioners have tried to apply the method as early as 12-13 weeks [70], 12-16 weeks [32] or 4-18 weeks [39]. Early assessment seems to integrate the disadvantage of a rather high false-positive rate. At 16 to 18 weeks, sensitivity was 68% with a specificity of 69% [16]. One intervention to reduce the high rate of false positives was the introduction of a two-stage screening, with a first scan at 18-22 weeks and a second scan of screening-positive patients at 24 weeks [9,22]. Meanwhile, most of the studies prefer assessment time of 18 to 24 weeks [11,12,17,24,27,45,47]– mostly as part of an “anomaly scan” - with the disadvantage of late onset of potential therapeutic interventions. Study data confirm the hypothesis [46] that the disadvantage of late diagnostic information of DSUA at 20 to 23 weeks is balanced by a reduction of the frequency of false positive results.

4.2.2 Definition and Registration of Outcome Variables

Another crucial point of evaluation is the definition of outcome variables [26]. One of the reasons not to accept DSUA as a routine procedure is the still incomplete agreement on the issue. Fetal hypoxia, gestational diabetes and operative delivery found entrance only into few studies [10,15,56,70] and were omitted in following evaluations. Most studies evaluated some of the complications such as pre-eclampsia, intrauterine growth retardation, preterm delivery, placental abruptio and IUD / NND. Apart from this study, 2 other studies [31,45] integrated all of these outcome variables.

While the duration of pregnancy, as well as the way of delivery and the birth-weight can be evaluated exactly, the occurrence of pre-eclampsia and placental abruptio are not amenable to an exact evaluation. The wide diversity of definitions, standards and subjective information are variables that influence the adverse outcome.

4.2.2.1 Pre-Eclampsia (PIH = Pregnancy Induced Hypertension PPIH = Proteinuric Pregnancy Induced Hypertension)

The outcome variable which is most frequently described, is pregnancy induced hypertension or pre-eclampsia, also described as proteinuric pregnancy induced hypertension. While few studies used pregnancy induced hypertension (PIH) [16,47] as an outcome variable, others only used proteinuric pregnancy induced hypertension (PPIH) [55,66,75] also described as pre-eclampsia [11,24,32,45,53,57,65] or all of these [10,17,50,70]. Pregnancy-induced hypertension has been defined as two recordings, 4 h apart, of diastolic blood pressure > 90 mmHg alone, or one reading of 110 mmHg or above [10] or systolic blood pressure > 150 mmHg [65]. Pre-eclampsia is defined as two recordings of diastolic blood pressure of $\geq$90 mmHg with proteinuria of >300mg [32], 400 mg/24h [12], 500 mg/24 h [70] or 1000 mg/24 h [65]. Severe pre-eclampsia is specified as blood pressure at least 160/100 or at least 140/90 in combination with other features like worsening proteinuria, thrombocytopenia, elevated liver enzymes and other symptoms [2].

Author	n	gestational week	definition of patho-logical. waveform		outcome variables	
Campbell et al. (1986) "improvement over existing predictive techniques"	126	16-18	Bilat Notch Unilat. Notch Impedance:? RI > 0,58	+ - +	Preeclampsia IUGR (< P'10) Preterm delivery Placental abruption IUD / NND **Fetal asphyxia**	+ + - - - +
Hanretty et al. (1989) "do not support the introduction of this new technique"	543	26-30 34-36	Bilat. Notch Unilat. Notch Impedance: ? A/B-ratio > P'95	- - +	Preeclampsia (PIH) IUGR (< P'5) Preterm delivery Placental abruption IUD / NND	+ + - - -
Newnham et al. (1990) "no role as screening test in low risk population"	535	18 24 28 34	Bilat. Notch Unilat. Notch Impedance: ? A/B > P'95	- - +	Preeclampsia IUGR (<P'10) Preterm deliv. (< 38 wks) Placental abruption IUD / NND ***Fetal hypoxia***	+ + + + - + +
Steel et al. (1990) "useful method of identifying a high risk group"	1014	16-22 24	Bilat. Notch Unilat. Notch Impedance: ? RI > 0,58	- - +	Preeclampsia IUGR (<P'5/<P'10) Preterm deliv. (<34/<37 wks) Placental abruption IUD / NND	+ + + - +
Davies et al. (1992) "no improvement in neonatal outcome"	2600	19-22	Bilat. Notch Unilat. Notch Impedance: best RI>P'95	- - +	Preeclampsia IUGR Preterm delivery Placental abruption IUD / NND	- - - - +
Bower et al. (1993) "preeclampsia can be predicted ...."	2058	18-22	Bilat. Notch Unilat. Notch Impedance: worst RI>P'95	+ + +	Preeclampsia IUGR Preterm delivery Placental abruption IUD / NND	+ - - - -
Bower et al. (1993) "a group of utero-placental compli-cations can be predicted"	2058	18-22	Bilat. Notch Unilat. Notch Impedance: worst RI>P'95	+ + +	Preeclampsia IUGR (<P'3/P'5/P'10) Preterm delivery Placental abruption IUD / NND	+ + - + +
North et al. (1994) "do not support... as a screening test in nullliparous women"	458	19-24	Bilat. Notch Unilat. Notch Impedance: 6 methods	+ + +	Preeclampsia IUGR (<P'10) Preterm delivery Placental abruption IUD / NND	+ + - + -
Chan et al. (1995) "overall performance is unsatisfactory"	334	20 28 36	Bilat. Notch Unilat. Notch Impedance: mean RI>P'90	+ - +	Preeclampsia IUGR (<2500g) Preterm delivery (< 37 wks) Placental abruption IUD / NND	+ + + - +

Van den Elzen et al. (1995) "do not permit the use of PI as screening test"	352	12-13	Bilat. Notch Unilat. Notch Impedance: ? PI > 1,67	- - +	Preeclampsia IUGR (<P'10) Preterm delivery (<38 wks) Placental abruption IUD / NND **Gestational diabetes**	+ + + - - +
Harrington et al. (1996) "patients with persistent bilateral notching are at risk"	1326	19-21	Bilat. Notch Unilat. Notch Impedance: combination	+ + +	Preeclampsia IUGR (< P'10) Preterm deliv. (<35 wks) Placental abruption IUD / NND	+ + + + +
Soutif et al. (1996) "contribution is doubtful in a low risk population"	315	19	Bilat. Notch Unilat. Notch Impedance: worst A/B>2,6	+ + +	Preeclampsia IUGR (< P'10) Preterm delivery Placental abruption IUD / NND	+ + - - -
Harrington et al. (1997) "may be of value"	652	12-16	Bilat. Notch Unilat. Notch Impedance: ? Elevated RI	+ - +	Preeclampsia IUGR (<P'10) Preterm delivery Placental abruption IUD / NND	+ + - + +
Irion et al. (1998) "Doppler does not qualify as screening test"	1159 (26 wks) ca 1000 (18 wks)	„around 26" + „around 18" (not presented)	Bilat. Notch Unilat. Notch Impedance: worst A/B ≥P'90 or RI > 0,58 or A/C ≥ 2,5	+ + +	Preeclampsia IUGR (<P '10) Preterm delivery (<38 wks) Placental abruption IUD / NND	+ + + - -
Kurdi et al. (1998) "addition of color Doppler ... may be of use"	946 (1022)	19-21	Bilat. Notch Unilat. Notch Impedance: Combination:	+ + +	Preeclampsia IUGR (< P'5) Preterm delivery Placental abruption IUD / NND	+ + - + +
Mires et al. (1998) " ...notching ... poor as a screening test"	6579	18-20 22-24	Bilat. Notch Unilat. Notch Impedance	+ + -	Preeclampsia IUGR (< -2SD) Preterm delivery Placental abruption IUD / NND	+ + - + -

Table 14: Overview of 19,374 patients of 16 studies concerning "low-risk" pregnancies (or "medium risk" pregnancies). Publications 6 and 7 were counted once because both described the same study group. Among "outcome variables", fetal asphyxia [16,56] and gestational diabetes [70] were separately mentioned because they were used only in three publications. Impedance = "?": publication does not show clearly whether uni- (better or worse side?) or bilateral (mean ?) assessment of uterine artery impedance is meant. "Combination" is defined as "Combination I" according to Tables 4-11.

With an incidence of 2.6% - 7%, pre-eclampsia is a frequent disease [10,71,72]. In the present study group, the prevalence of pre-eclampsia of 0.68% was low. This may be due to several reasons such as:

- low incidence (low risk collective)
- therapeutic interventions. In high risk pregnancies low dose Aspirin® commenced at 24 weeks may reduce the incidence of severe pre-eclampsia [11]. Although early onset of medication improves effect, also Aspirin® started at 24 weeks may have an effect [24]. The associated reduced pre-eclampsia rate would lead to an underestimation of the predictive values. Moreover, the predictive values used in this study were lower, as the values in a situation where the information about abnormal waveforms was not given to clinicians and no special follow-up was arranged [45].
- missing feedback of cases of pre-eclampsia. The patients in the study group were referred to the centre only for ultrasound examinations. All the information including the recording of pre-eclampsia of the study group were based on the forms completed by the patients. It can be assumed that patients feedback of pre-eclampsia was seen recorded only in severe cases that led to therapeutic interventions. One must therefore allow for the possibility that the prevalence of pre-eclampsia in the study group is underestimated and that the information concerning prevalence of pre-eclampsia and diagnostic value of abnormal uterine artery waveform concerning this outcome variable is not exact.

In the study group, “Combination 1” predicted 54.9% of all cases of pre-eclampsia, with a specificity of 93.4%. The registration of “any notching”, performed equally well indicating that the predictive value of “notching alone” is not improved by integrating elevated impedance as a predictor of pre-eclampsia. Using PI alone or “Combination 2” resulted in reduced specificity.

4.2.2.2 Placental Abruption

According to Table 14, 7 of the published studies integrated abruption of the normal positioned placenta as an outcome variable. While the incidence of all forms of vaginal bleeding (“more than an egg-cup full”) after 24 weeks was reported to be 3.7% [32] and 7.1% [56], the incidence of placental abruption was reported lower [4,9,31,56] ranging between 0.4% [45] and 1.05% [31]. In the study group 26 reported cases of placental abruption (0.35%) with the consequence of 7 cases of fetal demise (27%) were seen. No maternal death was reported.

Eleven cases (42.3%) were preceded by pathological waveform of DSUA according to the definition of “Combination 1”. The sensitivity of bilateral notching (34.6%) was lower than for “Combination 1”. Mean PI>P90 alone, predicted 38.5% of the cases with placental abruption, with a lower specificity of 90.2%. With the use of a combination of notch and elevated impedance, similar values to those that were observed in the study were obtained in an earlier study [31] with a sensitivity of 30.7% and specificity of 91.1% which performed better than notch alone (sensitivity of 15.3%, specificity 95.0%).

4.2.2.3 IUGR (Intrauterine Growth Restriction, Low Birth Weight, Placental Insufficiency, Fetal Growth Restriction

Low birth weight or fetal growth restriction was also used as an outcome variable in most of the relevant publications [3,10,15,16,17,24,32,45,53,55,57,66,67,75]. The problem of this outcome variable is the definition of normal values and weight percentiles. Studies describing the absolute birth weight [11] are not very informative because a shorter duration of pregnancy could be shown to be correlated with pathological uterine waveforms in mid-term pregnancy [20,45,70]. The normal values and centiles used to define fetal growth restriction in some of the studies were gained out of own evaluations, others used values of different cohorts [31,40,55,57]. IUGR usually was defined as a birth weight $<10^{th}$ centile [31,40,55,57] also $< 5^{th}$ centile [32].

This study decided to compare its findings with the values published by Yudkin [74]. Thus the study had 3.9% of fetuses with low birth weight, defined as birth weight of less than the 10'th centile according to Yudkin's definition. Since birth weight and duration of pregnancy were exact data, this low prevalence cannot be explained with missing or wrong feedback but must be due to different distributions of birth weight of normal pregnancies. Regarding birth weight, the study group seemed to be at low risk as compared to Yudkin's normal population. The fetuses / new-borns that were considered as having a low birth weight as per Yudkin's definition were those who had birth weights below the 4th percentile in the study target population. The definition used only regarded the cases of relevant growth restriction in the study population.

The predictive value of "Combination 1", with a sensitivity of 31.2% and a specificity of 94.0%, exceeded the performance of notching alone. With a sensitivity of 37.0% (specificity 91.2%), elevated impedance alone (mean PI>P90) performed equally well, indicating that the predictive capacity of elevated impedance alone might not be substantially improved by integrating any notching.

4.2.2.4 Preterm Delivery

Different authors defined preterm delivery as delivery prior to 38 weeks [37,56,70], 37 weeks [45] or 35 weeks [31]. The present study decided to perform the evaluation based on three definitions:

- delivery prior to 37 gestational weeks (n=338, 4.51%)
- delivery prior to 33 gestational weeks (n= 94, 1.25%)
- delivery prior to 29 gestational weeks (n= 31, 0.41%)

Integrating the group of deliveries between 33 and 37 weeks has the disadvantage of creating a rather large group of "complicated" pregnancy outcomes with the implication of a nowadays rather low morbidity and mortality of this group.

While some authors [17,37,56] did not find a correlation between pathological waveform and preterm delivery using definitions of preterm delivery of <37/<38 weeks, others [31,66] had positive results defining preterm delivery <34/<35 weeks. In the present study group, preterm delivery correlated with elevated impedance of uterine arteries. This may be due to several reasons such as:

- patients at risk had a therapeutic preterm delivery to prevent complications
- elevated impedance per se is known to induce preterm delivery [67]. “Combination 1” and PI yielded a higher sensitivity for the prediction of preterm delivery, both before 33 and 29 weeks, than notching alone. The use of PI alone, however, yielded a worse specificity. Overall, the combination of elevated impedance and notching (“Combination 1”) performed better than each of the parameters notching and elevated impedance alone.

4.2.2.5 Perinatal Mortality (IUD = intrauterine death, NND = neonatal death)

Seven of seventeen publications in Table 14 integrated IUD / NND as an outcome variable. The present study observed 20 cases, leading to a perinatal mortality of 0.27% (2 IUD’s <29weeks, 14 IUD’s>28 weeks, 4 cases of neonatal death). This rate is low compared with perinatal mortality rates of other publications within study groups of more than 1,000 pregnancies, ranging between 0.77% [22] and 2.75% [20]. This may be due to the low-risk character of the study population, the exclusion of the major part of severe congenital anomalies, and the fact that information about abnormal waveforms caused therapeutic interventions. The aim of the extended sonography, including DSUA, is a reduction of perinatal mortality. The predictive value concerning this outcome variable should be low, because as a result of the detection of elevated risk, the IUD / NND should be prevented. Patients and physicians were informed about the results of DSUA and came to therapeutic conclusions. Still, in the study group 4 fetuses with pathological waveforms were lost (“Combination 1”) at 20-23 weeks DSUA, at 27, 28, 29 and 40 weeks. With the experience of today and the results of the study, the demise of three of them would be preventable in the future.

In the prediction of IUD / NND, “Combination 1”, with a sensitivity of 20.0% and a specificity of 93.1%, performed better than notching only and PI only. Also, here the combination of elevated impedance and notching performs better than each of the parameters notching and elevated impedance alone.

4.2.3 Therapeutic Interventions

The ultimate goal in the management of pre-eclampsia, is to be able to detect the disease in the early stages and have available a therapy, that either cures it or at least ameliorates its progression in an attempt to achieve fetal maturity [23]. Ideally, early identification of patients at risk for pre-eclampsia and their effective treatment would permit the safe completion of pregnancy for the mother and her infant [25]. There is considerable disagreement about the value of DSUA, and its therapeutic consequences, especially the effectiveness of low dose Aspirin®. While some authors do not see positive effects [20,54], others [11,24,50] describe a significant reduction of complications like pre-eclampsia and IUGR if used properly (early onset of therapy, correct dose, correct definition of risk groups). It has to be stressed that there are several options for clinical management such as:

- low dose Aspirin® [11,24,33,50]
- medications other than Aspirin® [25]
- intensive observation
- premature maternity leave
- intensive care with the option of timely intervention in the form of preterm delivery, before intrauterine death [2].

Whether or not Aspirin® or premature maternity leave is helpful still remains unclear. At least it can be expected that the effect of these diagnostic and therapeutic interventions – if present – would be an improvement to the pregnancy outcome with respect to fetal growth restriction and IUD / NND. The outcome of those patients at risk, not using the information provided by DSUA would be worse. The effect on

duration of pregnancy may be significant because of the prevention or the delay of the onset of problems. On the other hand, however, it is also possible that the more intensive care of risk patients may result in a shorter pregnancy duration because of timely intervention in the interest of both mother and fetus.

The present study was not designed to answer the question of efficacy of any prophylactic medication. One of the reasons for missing the effect of prophylactic medication in earlier studies was the insufficient selection of patients through an appropriate test. In this regard the data presented here may be helpful in identifying patients of a presumed low-risk group, that in fact is at high risk for major complications.

4.2.4 Definition of Abnormal Waveform

Although it seems to be accepted that pathological waveform of uterine artery/arteries may predict adverse pregnancy outcome, there is no agreement about the definition of such pathological waveforms. In the beginning, only high impedance was important [16,22]. Also, bilateral notching was taken into account [52]. Later studies described “pathological waveform” as the presence of either high impedance in form of high PI, RI or A/B-ratio, or the presence of a “notch” in one or both uterine arteries [10,11,17,65,75] or a combination of both [31,32,33].

Regarding impedance alone, it is not completely clear in many publications whether the impedance was evaluated on one side (the better / worse?) or if the mean of both sides was evaluated [12,16,75]. The best results were achieved by using the mean impedance of both uterine arteries [47]. A reduction of the predictive value was reported if the impedance of only the better - [22,57] (“unilateral good perfusion is sufficient”) or the worse uterine artery [11,65] was used. These results are confirmed in the present study. In a prospective randomised trial regarding the impedance of the better of the two uterine arteries alone, no improvement of neonatal outcome could be shown [22]. Presence of notch alone was found to be a better predictor than elevated impedance alone [10].

Meanwhile, it seems to be clear that both presence of notch in one or two uterine arteries as well as high impedance seem to correlate with adverse pregnancy outcome.

The study data seem to confirm the hypothesis that at 20-23 weeks, the best performance of the method may result from a combination of notching and impedance [32,33]. Bilateral notching predicted adverse outcome in combination with a relative low mean impedance (> 50’th centile). On the other hand, without any notching, high resistance of both uterine arteries (>95’th centile) was predictive. Unilateral notching predicted adverse outcome, if mean impedance exceeded the

90’th centile. Regarding the presence of uni- or bilateral notch alone or impedance parameters alone resulted in reduced performance of the test.
Few authors have tried to define a notch as a “definite upward change in velocity after the initial deceleration slope of the primary wave” [27,52] or as “clearly visible lower early diastolic velocities when compared to mid-diastole” [75]. This definition discriminates in most cases between the presence and absence of a notch. In borderline cases with slight upward change (“unstable notch” [75]), the reproducibility of notch seems to be variable. Concordance of detection of notching of two operators of only 85% has been reported [10], and disagreement of unilateral notching has been found in 9.8% and bilateral notching in 6.8% [27].

In this study, the method used to find a clear definition of presence or absence of notch was the introduction of NI: D-C/D. Few publications have tried to quantify notching [1,12,13,36,57,69]. Whether or not any quantification of the notch, by using various proposed definitions, improves the diagnostic capacity of DSUA, is unclear and requires further research. There is evidence that the predictive value of quantification of notch compared with PI appears to be relatively low [46].

There is still disagreement regarding the optimum time of examination, since impedance of uterine arteries is highly dependent on stage of pregnancy [8,39]. Likewise, not all authors agree with the concept of evaluation of the mean resistance of both uterine arteries, therefore, normal values of vascular resistance are not available or are not described in detail [11]. Table 2 shows that there is a weekly difference in the normal range of flow impedance

The data in Table 2 shows that to reach optimal performance it is not necessary to use a uniform value for the whole time span studied [34] but to establish normal values of mean impedance week by week, and to describe them to achieve the possibility of comparing different studies at least in the overlapping phases of pregnancy.