2. PATIENTS AND METHODS

2.1 Patients

Data from consecutive unselected women presenting for a routine anomaly scan between 20+0 and 23+6 gestational weeks were retrieved for a period ranging from January 1993 to August 2000. DSUA was performed as a routine part of the "anomaly scan". Multiple pregnancies, pregnancies ending in spontaneous abortion prior to 25 gestational weeks or in termination were excluded, as well as ongoing pregnancies complicated by malformations not compatible with postnatal life which were detected before 25 weeks. Each patient entered the study only once. Subsequent pregnancies of the same patient were excluded.

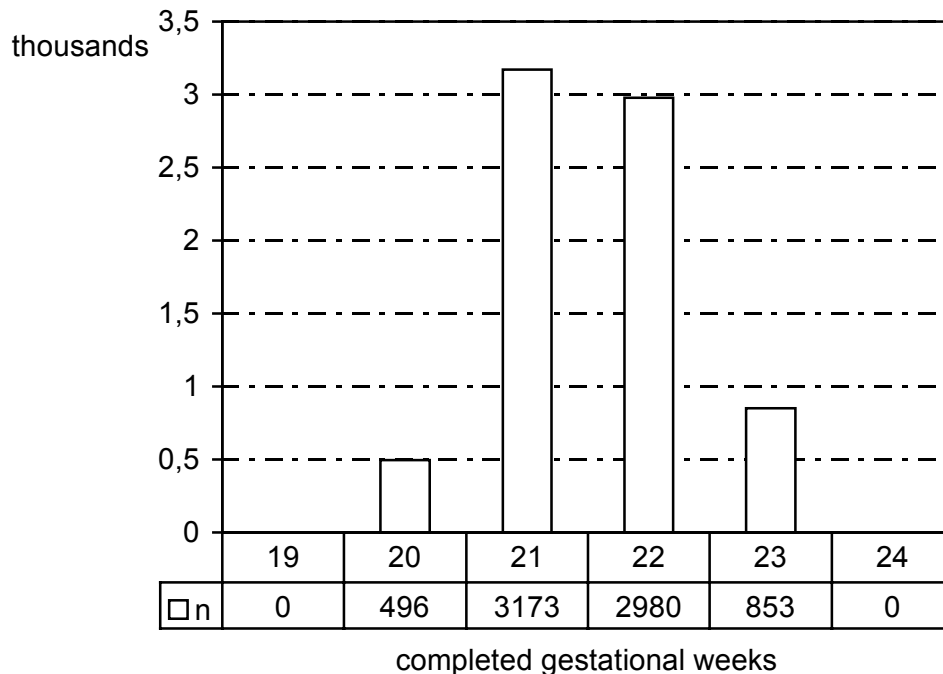The time of assessment is shown in Figure 1.

	19	20	21	22	23	24
□ n	0	496	3173	2980	853	0

completed gestational weeks

Figure 1: **Gestational Age at Doppler Screening:** Distribution of Patients Between 20 and 23 Completed Gestational Weeks (n=7,502)

The age distribution in the screened population is demonstrated in Figure 2. The median according to the age of the pregnant women was 31 years (15 - 47).

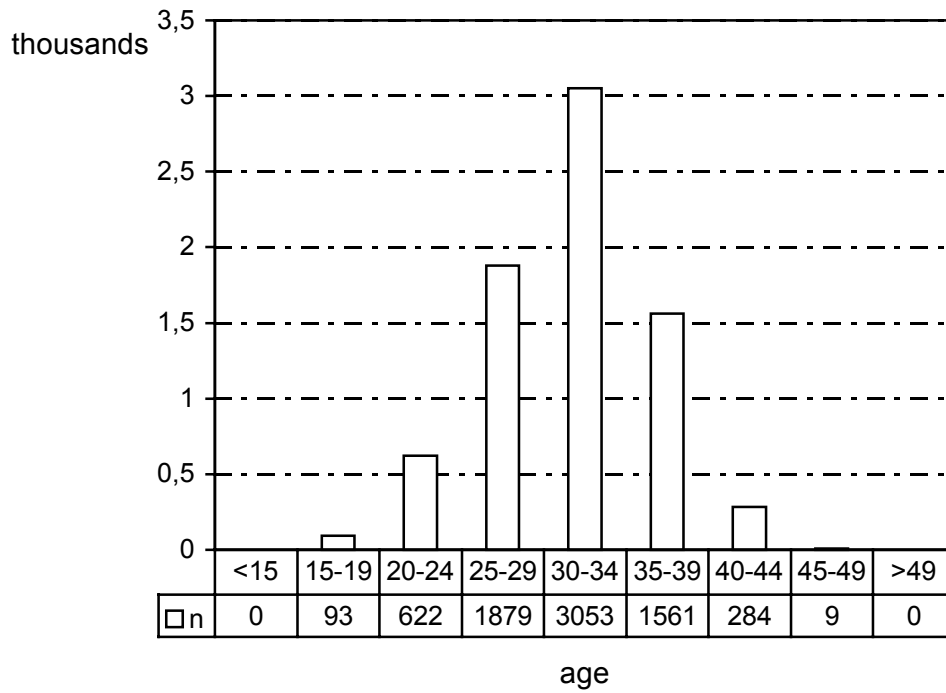|	<15	15-19	20-24	25-29	30-34	35-39	40-44	45-49	>49
□ n	0	93	622	1879	3053	1561	284	9	0

age

Figure 2:   **Age** Distribution of all Pregnant Women (n=7,502)

The body size distribution in the screened population is demonstrated in Figure 3. The median according to the body size of the pregnant women was 168 cm (145 - 191)
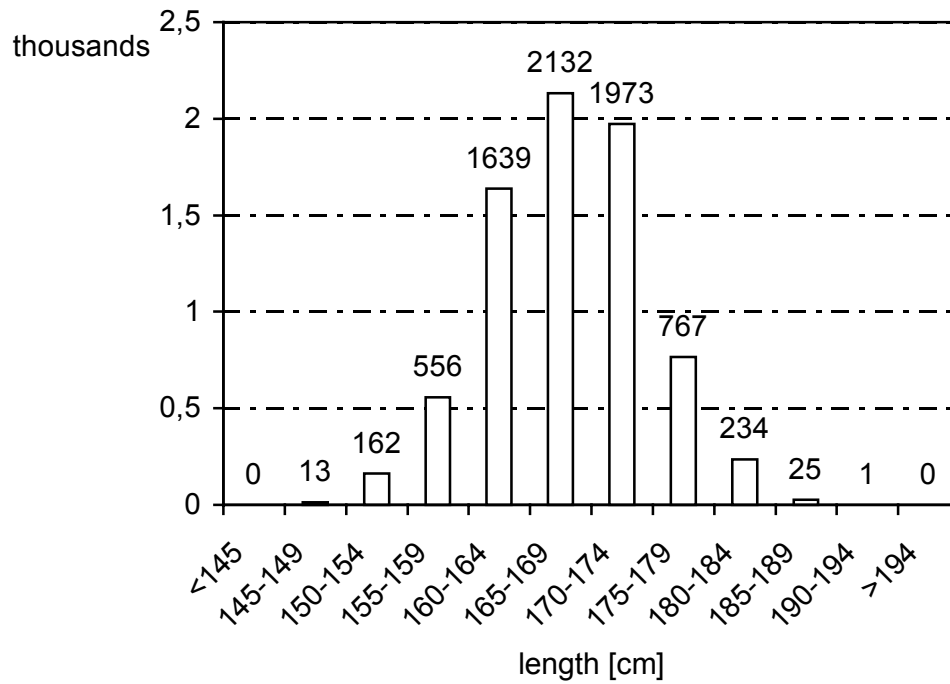

Figure 3:   **Body size** Distribution of all Pregnant Women (n=7,502)

The body weight distribution in the screened population is demonstrated in Figure 4. The median according to the body weight of the pregnant women was 66 kg (42 - 150).
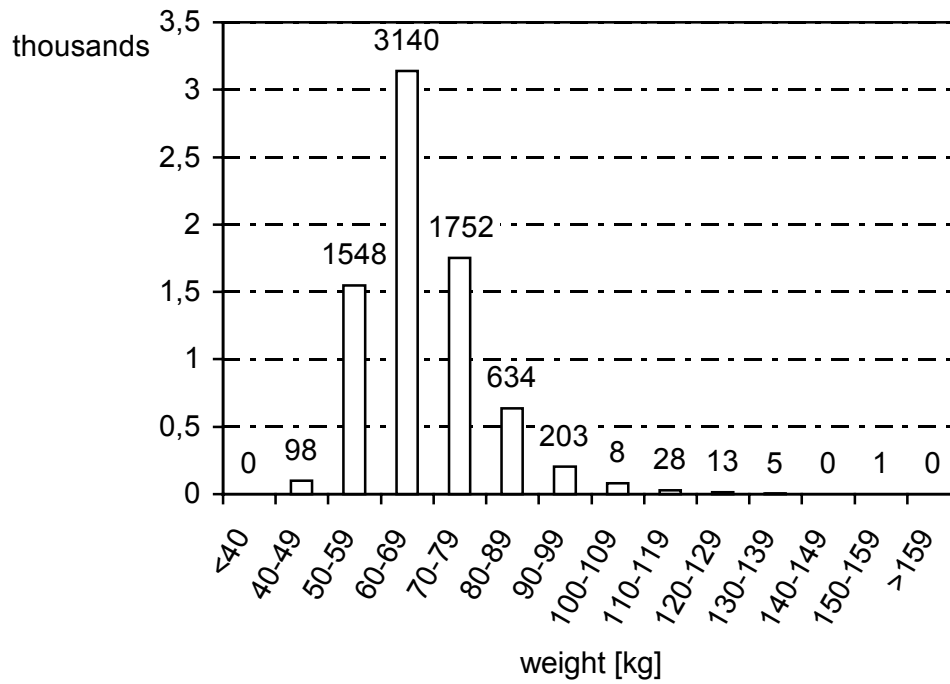
Figure 4:   **Body Weight** Distribution of all Pregnant Women (n=7,502)

An important factor, that could possibly influence the result of the screening method was the presence of increased body weight or obesity of the patients. The Body Mass Index (Quetelet-Index) of the target population can be seen in Figure 3. The Quetelet-Index was calculated according to the body weight and the size of the patients following the equation:

$$\frac{weight \quad [kg]}{square \ size \quad [m^2]} = \textbf{\textit{BMI}}$$

The Body Mass Index distribution in the screened population is demonstrated in Figure 5. The median for the BMI of the pregnant women was 23.34 (15.37 - 48.44)

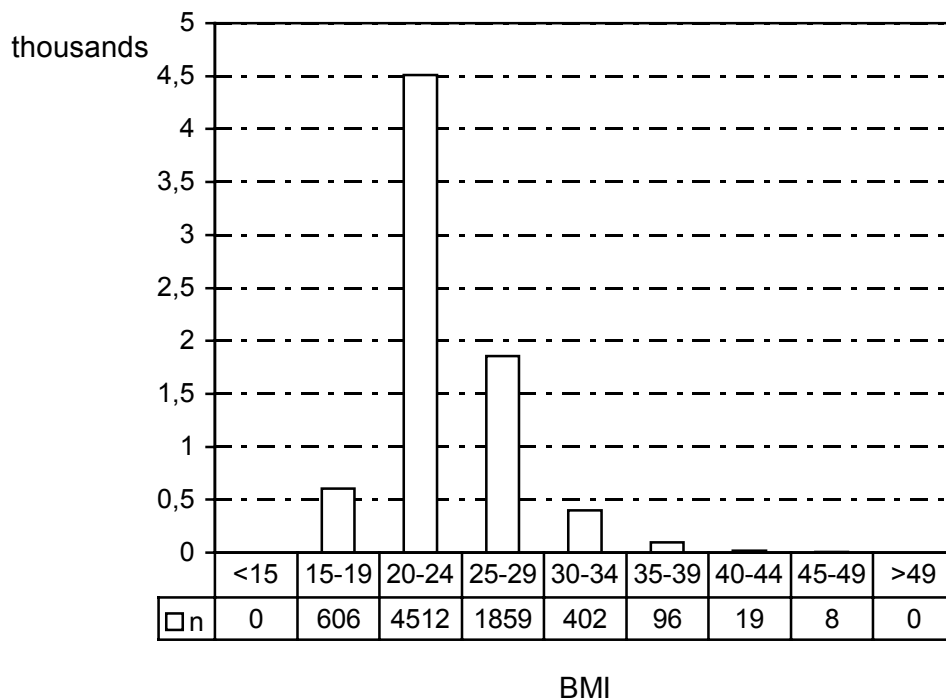|	<15	15-19	20-24	25-29	30-34	35-39	40-44	45-49	>49
□ n	0	606	4512	1859	402	96	19	8	0

BMI

Figure 5: **Body Mass Index** (BMI), Quetelet-Index of all Pregnant Women (n=7,502)

2.2   Method of Examination

The institution where all the examinations were performed was a non-university ambulant office serving as a referral centre for more than 200 gynaecologists. Annually an average of 14,000 sonographic examinations are performed at this centre. The experience of all examiners involved in this study was at least 5 years of exclusive ultrasonographic work. Data on the examinations were registered by specially trained midwives accompanying each examination using a computerised registration system.

Ultrasonic examination was performed with an ACUSON XP10 (ACUSON, Mountain View, CA, USA) equipped with colour and pulsed Doppler capabilities. Flow velocity waveforms of the right and left uterine arteries were imaged at 20 – 23 completed weeks of gestation. With the patient semi recumbent, the iliac artery was identified in the lower abdominal quadrant, lateral to the uterus. The transducer was than angled medially, and the uterine artery was identified with colour flow Doppler imaging. The recording was performed at the crossing of the uterine and the external iliac arteries. This is an intersection that is present apparently only in pregnancy, because the enlarged uterus moves the main uterine artery to a more lateral position. This virtual crossing is the most useful position to identify the main uterine artery and it reduces the risk of recording the Doppler waveforms of unreliable places in different patients. Insonation of the artery with pulsed Doppler imaging was than performed.

Impedance of the uterine arteries was measured using the definition of resistance index (RI) and pulsatility index (PI). To find an objective way of defining the presence of a notch, a "Notch-Index" (NI) with a definition similar to RI was used. Notch-Index was defined as (C-D)/C with D=post-systolic nadir and C=following zenith of the waveform. A definition of a waveform as complicated by notch if NI exceeded a value of 0.05, was used.
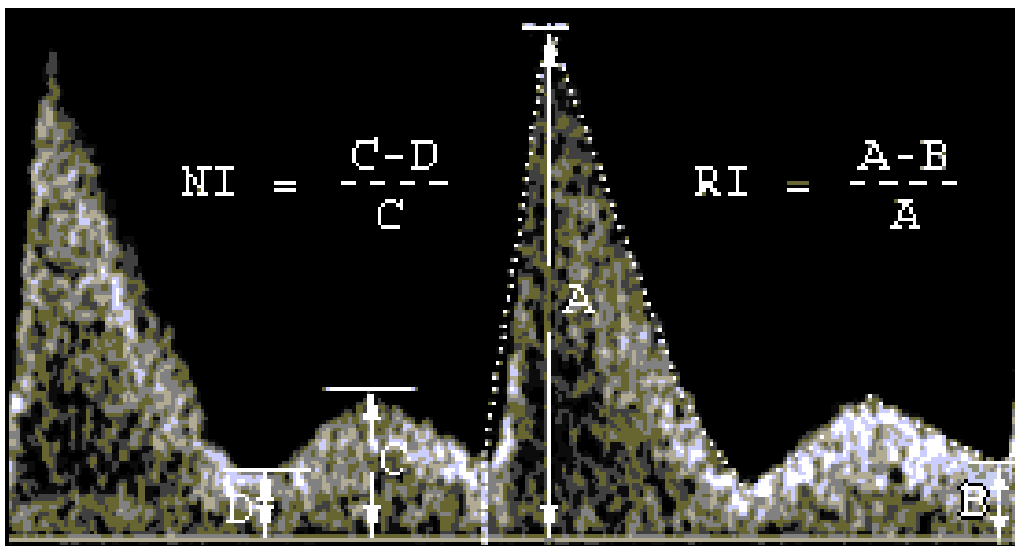

Figure 6:   Definition of **"Notch Index"** (NI)

2.3   Evaluation

The previous criteria were fulfilled by 8,244 patients. Feedback on the outcome of 7,502 of these pregnancies (91%) were obtained. Only these data were evaluated.

<u>Definition of Abnormal Waveform</u>

For the retrospective analysis, the screening efficacy of DSUA (as determined by the sensitivity, specificity, and the positive and negative predictive values) was assessed using four definitions of pathological waveform:

  I.   **Presence of uni- or bilateral notch:** A notch was defined as a situation where the post-systolic lowest point of the waveform reached a velocity that was at least 5% lower than the following mid-diastolic peak velocity.

  II.   **Elevated impedance** of the better (minimum), worse (maximum) or mean of both uterine arteries exceeding the 90th percentile of the "normal population" using the Pulsatility Index (PI).

  III.   **"Combination 1":** Waveforms of the uterine arteries were defined as pathological if

- there was no notch on both uterine arteries and the mean of the PI-values of right and left uterine artery (and the mean PI value of both uterine arteries) exceeded the 95th centile of the "normal population"
- there was a unilateral notch and the mean of the PI-values of right and left uterine artery exceeded the 90th centile
- there was a bilateral notch and the mean of the PI-values of right and left uterine artery exceeded the 50th percentile. This combination is comparable to that used by Kurdi et al. [45] and Harrington et al. [33], with the exceptions that PI instead of RI was used, and that impedance values for each gestational week were adjusted and that a reproducible definition of notch was used.

IV. **<u>"Combination 2":</u>** Waveforms of the uterine arteries were defined as pathological if

- there was no notch on both uterine arteries, and the mean of the PI-values of right and left uterine artery exceeded the 90th percentile of the "normal population"
- if there was unilateral notch and the mean of the PI-values of right and left uterine artery exceeded the 50th percentile
- if there was bilateral notch independent of impedance values.

<u>Feedback</u>

Each patient was asked to send back a form containing information about date, way and place of delivery, sex and weight of the fetus / new-born as well as complications of pregnancy and delivery. In case of missing feedback until 30 days after the estimated date of delivery, patients were contacted by telephone. During the years 1999 and 2000 the rate of active (sent by the mothers) and passive (information by telephone) feedback was recorded. In these years, 1,270 of 2,097 patients (60,6%) had to be contacted by telephone. It was assumed that the frequency of passive feedback might be similar for the whole study period.

<u>Outcome Variables</u>

The main outcome variables for this analysis were, gestational age at delivery; development of pre-eclampsia; delivery of an intrauterine growth retarded (IUGR) baby; placental abruption and intrauterine death (IUD); or neonatal death (NND) within the first 7 days of life. "Any" complication included any case with pre-eclampsia, placental abruption, delivery of an IUGR baby, premature delivery, or IUD / NND, or some of these.

Premature Delivery

Premature delivery was defined as delivery, spontaneous or by intervention, before 29 (= 27+7) or 33 (= 31+7) gestational weeks, respectively.

IUGR

The definition of being IUGR (< 10th centile) at birth was based on the table published by Yudkin et al. [74].

Normal Values

Normal values of minimum, maximum and mean PI of both uterine arteries were obtained by evaluation of the total study population independent of the pregnancy outcome.

Statistical Assessment

The evaluation of our data was performed using SAS®.

Therapeutic Consequences

During the study time, uterine artery waveforms were regarded as pathological in presence of bilateral notch or in case of bilateral high impedance with or without unilateral notch. Each patient was informed about the result of the examination. In case of waveforms that were thought to be pathologic, medication of 100 mg Aspirin® per day upon on an arbitrary basis without using one of the clear definitions listed above was recommended. In 157 cases, the advice of taking this medication was

followed by the patients; in further 88 cases, the medication was recommended; it remains unclear whether the patient followed the advice or not. If a pathological waveform was detected, a control examination at 26 to 30 weeks was recommended depending on the degree of abnormality of Doppler velocity waveform. Further interventions depended on the clinical situation.