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MATERNAL-FETAL MEDICINE

First trimester uterine artery pulsatility index levels in euploid and aneuploid pregnancies

Natalia Prodan[1] · Philipp Wagner[1] · Jiri Sonek[2,3] · Markus Hoopmann[1] · Armin Mutz[1] · Sara Brucker[1] · Karl Oliver Kagan[1]

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Abstract

Objective To examine whether the uterine artery PI is different in aneuploid and euploid pregnancies.

Methods Retrospective case-matched study at the department of prenatal medicine at the University of Tuebingen, Germany. The study involved patients with complete data on first trimester screening for trisomies and preeclampsia except PlGF. For each case with trisomy 21 we randomly selected 50 cases with a euploid fetus where complete data on screening for aneuploidy and preeclampsia were also available. The uterine artery pulsatility index and the corresponding MoM values of euploid and the aneuploid population were compared with a Man–Whitney *U* test.

Results The dataset consisted of 4591 singleton pregnancies. The karyotype was normal in 4500 cases and was abnormal in the remaining 91 pregnancies. There were 50 pregnancies with trisomy 21, 31 with trisomy 18 and 13, and 10 with triploidy. In the group with euploid fetuses, median uterine artery PI was 1.55 (0.99 MoM). In the group with trisomy 21, the median PI (1.42) and MoM (0.89) levels were both significantly lower than in the euploid ($p < 0.001$). However, the measurements in the trisomy 18 and 13 [1.61 (0.93 MoM)] and in the triploidy [1.99 (1.13 MoM)] groups were not significantly different from those in the euploid group ($p = 0.468$ and $p = 0.632$, respectively).

Conclusion In conclusion, uterine artery PI levels in the first trimester are slightly lower in pregnancies with trisomy 21. This knowledge may prove to be useful in cases where a low PAPP-A level is seen on the first trimester maternal serum biochemical evaluation to differentiate whether the more likely cause for this finding is placental dysfunction or aneuploidy, specifically trisomy 21.

Keywords Uterine artery doppler · Preeclampsia · Trisomy · First trimester

Introduction

Even with the availability of cell-free DNA (cfDNA) screening for chromosomal abnormalities, first trimester ultrasound and maternal serum biochemical marker measurement continue to be an important examination in pregnancy. It improves the detection of a large proportion of rare chromosomal abnormalities that are not detectable by cfDNA and results in the detection of about half of all major fetal structural defects. It also serves to predict maternal complications during the subsequent course of the pregnancy such as preeclampsia (PE) [1, 2].

The most efficient risk determination for PE is based on maternal history, biophysical markers such as the mean arterial blood pressure and the pulsatility index of the uterine artery (ut-a PI) Doppler, and maternal serum biochemical markers, such as PLGF and PAPP-A [3]. Using this model, O'Gorman et al. reported on a detection and false positive rate of 70% and 10%, respectively, for preterm preeclampsia [4]

Reduced PAPP-A levels are important for both screening for preeclampsia and for screening for trisomy 21, 18 and 13. However, in the majority of cases, low PAPP-A values are a normal variant without adverse outcome. Staboulidou et al. suggested that low PAPP-A should be

✉ Karl Oliver Kagan
KOKagan@gmx.de

1 Department of Obstetrics and Gynaecology, University of Tuebingen, Calwerstrasse 7, 72076 Tübingen, Germany

2 Fetal Medicine Foundation USA, Dayton, OH, USA

3 Division of Maternal Fetal Medicine, Wright State University, Dayton, OH, USA

followed by an examination of the ut-a PI [5]. High ut-a PI would suggest that the etiology for the low PAPP-A is more likely to be related to impaired placentation rather than aneuploidy. While many studies have demonstrated that in pregnancies where high ut-A PI correlates with an increased risk for preeclampsia, there are only a few studies that have looked at a possible association between uterine artery Doppler measurements and risk of chromosomal abnormalities.

In this study, we set out to examine whether the ut-a PI is different in aneuploid and euploid pregnancies.

Methods

This is a retrospective case-matched study involving patients that were seen at the department of prenatal medicine at the University of Tuebingen, Germany.

At our department, an ultrasound examination at 11–13 weeks' gestation always includes the following elements: CRL and NT measurement, nasal bone, ductus venosus and tricuspid blood flow assessment using Doppler as well as a thorough anatomical fetal assessment [6–9]. Maternal serum free beta-hCG and PAPP-A measurements are a routine component of our first trimester combined screen. In cases that are referred to us for invasive testing or where fetal defects or increased nuchal translucency is present, serum markers are not routinely measured.

In our clinic, we routinely perform first trimester screening for preeclampsia. The risk assessment is based on personal history, maternal characteristics, measurement of the ut-a PI, mean maternal arterial pressure, and maternal serum PAPP-A levels. Pregnancy and outcome data are recorded in a digital database (Viewpoint, GE Healthcare, Muenchen/Germany).

We searched our digital database for all cases with trisomy 21, 18 13 and triploidy where complete data on first screening for aneuploidy and screening for preeclampsia were available. For each case with trisomy 21 we randomly selected 50 cases with a euploid fetus where complete data on screening for aneuploidy and preeclampsia were also available. Women in either group who developed preeclampsia during the subsequent course of pregnancy were excluded from the study.

To evaluate a possible association between PAPP-A levels and ut-a PI, we selected a subset of pregnancies from the euploid pregnancies where the maternal serum PAPP-A levels were similar to those in the pregnancies with trisomy 21. For each trisomy 21 case, five euploid pregnancies with similar PAPP-A levels were selected.

The study was approved by the ethical committee of Tuebingen, Germany (No. 350/2019BO2).

Statistical analysis

The uterine artery pulsatility index, the mean arterial blood pressure and the serum markers were transformed into MoM values based on the current FMF algorithms. For the uterine artery PI transformation, the relevant covariates are: maternal age, maternal weight, cigarette smoking status, crown rump length and ethnic origin [10]. The uterine artery pulsatility index and the corresponding MoM values of euploid and the aneuploid population were compared with a Man–Whitney *U* test after exclusion of a normal distribution with a Kolmogorov–Smirnov test. Results are shown as median with interquartile range. Statistical significance was set at *p* level of 0.05.

Results

The dataset consisted of 4591 singleton pregnancies. The karyotype was normal in 4500 cases and was abnormal in the remaining 91 pregnancies. There were 50 pregnancies with trisomy 21, 31 with trisomy 18 and 13, and 10 with triploidy.

Median maternal age and gestational age were 33.6 years and 12.7 weeks, respectively. Median BMI was 23.8 kg/m^2. In 4470 (97.4%) cases, maternal ethnicity was Caucasian. 135 (2.9%) women smoked cigarettes and 199 (4.3%) pregnancies were the result of assisted reproduction techniques. 72 (1.6%) women had chronic hypertension prior to pregnancy. In 81 (1.8%) cases, the previous pregnancy ended in preeclampsia. Pregnancies that were complicated by preeclampsia during the subsequent course of this pregnancy were excluded. Further maternal details are shown in Table 1.

Fetal details are shown in Table 2. In the normal group and in the trisomy 21, trisomy 18 and 13 and triploidy group, median fetal NT thickness was 1.8, 3.3, 4.0 and 1.5 mm, respectively. Free beta-hcG and PAPP-A levels were as follows: 0.98 MoM and 1.09 MoM (euploid group), 2.25 MoM and 0.61 MoM (trisomy 21 group), 0.34 MoM and 0.30 MoM (trisomy 18 and 13 group), and 0.15 MomM and 0.14 MoM (triploidy).

In the group with euploid fetuses, median ut-a PI was 1.55 (0.99 MoM). In the group with trisomy 21, the median PI (1.42) and MoM (0.89) levels were both significantly lower than in the euploid ($p < 0.001$). However, the measurements in the trisomy 18 and 13 [1.61 (0.93 MoM)] and in the triploidy [1.99 (1.13 MoM)\] groups were not significantly different from those in the euploid group ($p = 0.468$ and $p = 0.632$, respectively). Figures 1 and 2 show the

Table 1 Pregnancy characteristics of the study population

	Normal	Trisomy 21	Trisomy 18&13	Triploidy
n	4500	50	31	10
Maternal age in years median (25 – 75th centile)	33.6 (30.6–36.5)	37.7 (35.8–40.3)	37.8 (35.2–39.9)	31.1 (29.5–32.5)
Gravidity in *n* median (25 – 75th centile)	2 (1–3)	2 (2–3)	2 (1–3)	1 (1–3)
Parity in *n* median (25 – 75th centile)	1 (0–1)	1 (0–1)	1 (0–1)	0 (0–2)
BMI in kg/m^2 median (25 – 75th centile)	23.8 (21.5–27.3)	23.4 (21.3–25.5)	24.5 (22.1–25.1)	24.8 (21.9–27.0)
Maternal weight in kg median (25 – 75th centile)	65.0 (59.0–73.6)	67.2 (61.0–74.0)	66.8 (59.2–70.0)	70.2 (57.0–73.5)
Caucasian ethnicity *n* (%)	4382 (97.4)	50 (100)	29 (93.5)	9 (90)
IVF / ISCI *n* (%)	194 (4.3)	3 (6.0)	2 (6.5)	0 (0)
Cigarette smoking *n* (%)	130 (2.9)	2 (4.0)	3 (9.7)	0 (0)
Arterial hypertension *n* (%)	71 (1.6)	1 (2.0)	0 (0)	0 (0)
Previous preeclampsia *n* (%)	80 (1.8)	0 (0)	1 (3.2)	0 (0)

Table 2 First trimester risk markers in euploid and aneuploid pregnancies

	Normal	Trisomy 21	Trisomy 18&13	Triploidy
Crown-rump length in mm median (25–75th centile)	67.6 (62.8–72.6)	66.2 (59.2–73.1)	58.7 (53–67.5)	54.1 (51.6–64.4)
Nuchal translucency in mm median (25–75th centile)	1.8 (1.6–2.1)	3.3 (2.7–5.4)	4.0 (2.3–5.7)	1.9 (1.5–3.4)
free beta hCG in MoM median (25–75th centile)	0.98 (0.68–1.47)	2.25 (1.48–3.31)	0.34 (0.23–0.7)	0.15 (0.06–0.71)
PAPP-A in MoM median (25–75th centile)	1.09 (0.77–1.47)	0.61 (0.4–1.01)	0.30 (0.18–0.59)	0.14 (0.04–0.6)
Mean arterial pressure in mmHg median (25–75th centile)	86.8 (80.8–93.2)	87.1 (79.6–93.4)	86.1 (78.7–97.3)	84.8 (83.8–97.3)
Mean arterial pressure in MoM median (25–75th centile)	1.02 (0.95–1.09)	1.01 (0.92–1.09)	1.00 (0.95–1.16)	0.98 (0.92–1.16)
Uterine artery Doppler in PI median (25–75th centile)	1.55 (1.30–1.86)	1.42 (1.22–1.56)	1.61 (1.37–1.89)	1.99 (1.66–2.19)
Uterine artery Doppler in MoM median (25–75th centile)	0.99 (0.84–1.19)	0.89 (0.77–1.03)	0.93 (0.81–1.17)	1.13 (0.93–1.34)

distribution of PI measurements and MoM levels according to karyotype.

The subset of patients designed to evaluate whether there is a correlation between PAPP-A levels and uterine artery PI measurements included 250 cases from the euploid group and the 50 cases with fetal trisomy 21. The median PAPP-A levels were similar in both groups: 0.61 (IQR 0.39–1.05) MoM and 0.61 IQR (0.40–1.01), respectively. However, the median uterine artery PI in the euploid subgroup [1.64 (IQR 1.34–1.96); 1.04 MoM (IQR 0.86–1.26)] was significantly higher than in the cases with fetal trisomy 21 (PI:1.42 [IQR 1.22–1.56]; MoM: 0.89 [IQR 0.77–1.03]) ($p < 0.0001$).

Discussion

In this study, we have compared the pulsatility index of the uterine arteries in euploid and aneuploid pregnancies. We found that in pregnancies with fetuses affected by trisomy 21, the impedance to flow was significantly lower than in the euploid population. This was the case even after correction for lower PAPP-A levels in fetuses with trisomy 21.

Some of our data are similar to those in previous studies. Bindra et al. examined the uterine artery PI in 613 euploid and 79 aneuploid pregnancies. They found similar PI levels for normal group and for pregnancies with trisomy 18 and 13 [11]. However, in this study, the pregnancies affected by trisomy 21 had essentially the same Ut-A PI as the euploid pregnancies. Staboulidou et al. compared the uterine artery PI of chromosomally abnormal pregnancies with the PI in pregnancies with subsequent early and late preeclampsia. The authors computed MoM levels to account for maternal and pregnancy characteristics such as ethnicity, body mass index and parity [12]. In the early and late preeclampsia group, the PI levels were 1.52 and 1.20 MoM, respectively, while in group of fetuses with trisomy 21, 18 and 13 and triploidy, the levels were 1.02, 1.20, 1.24 and 1.20 [5]. In contrast, our study demonstrated a decreased UtA-PI in trisomy 21 pregnancies only, with trisomy 13 and 18 pregnancies and those with triploidy showing no difference. Why our results differ from the results from the two previous studies from Kings College Hospital is unclear. We assume that

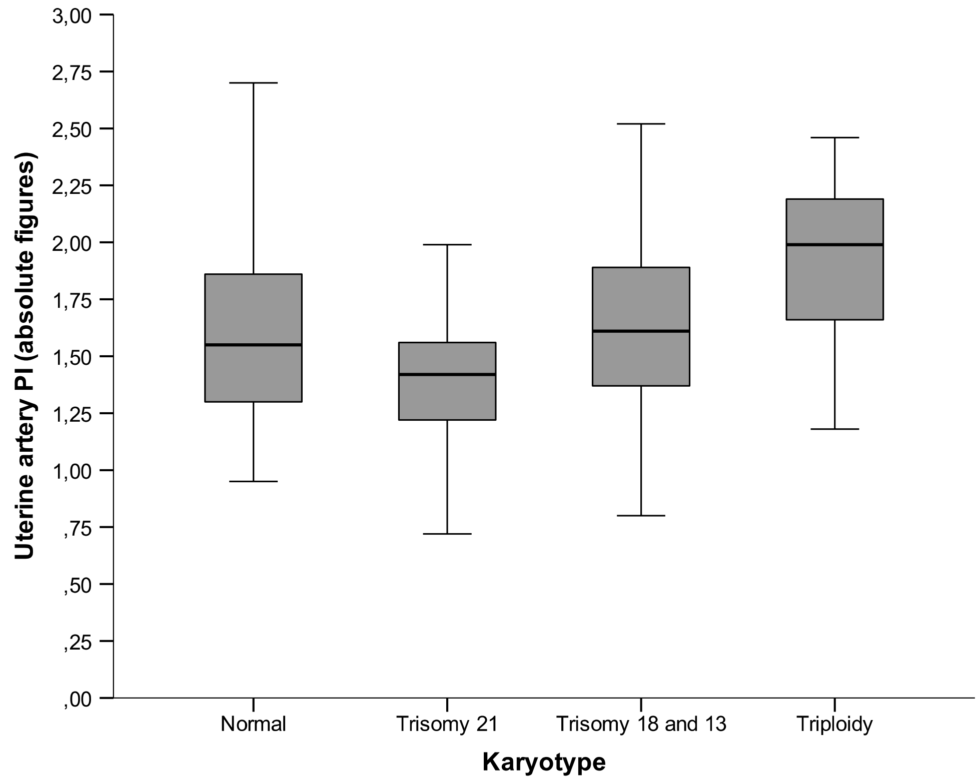

Fig. 1 Pulsatility index in euploid and aneuploid pregnancies

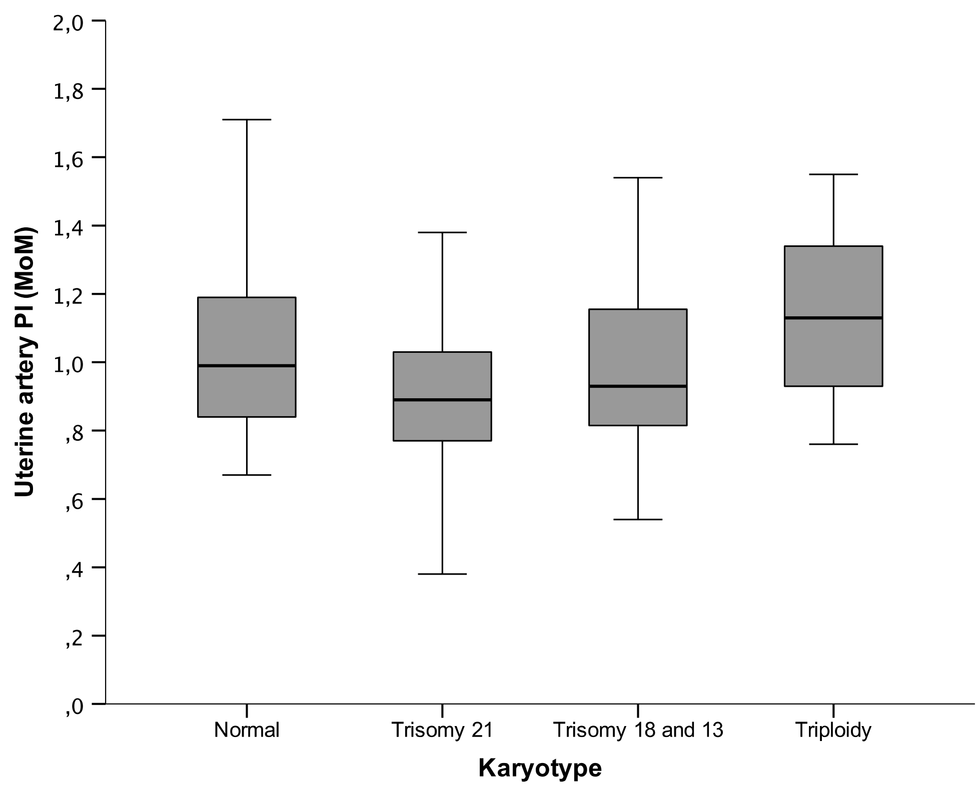

Fig. 2 Pulsatility index in MoM levels in euploid and aneuploid pregnancies

the differences between the studies are related to the small number of trisomic cases in each study.

Despite these inconsistent results, taking into account the ut-A PI measurement may still be beneficial in interpreting the results of those first trimester combined screens where the PAPP-A level is low. In their paper, Staboulidou et al. suggested that if in these cases the impedance is high, it is more likely that the low PAPP-A indicates an increased risk for preeclampsia rather than increased risk for aneuploidy [5]. The results of our paper support this approach. Our data suggest that this may be especially true in cases where there is an increased risk for trisomy 21.

Herraiz et al. examined whether there is a correlation between the uterine artery PI and other first trimester markers. The authors reported on a negative linear correlation between the PI levels and PAPP-A [13]. In the original paper from Plasencia et al. using MoM transformation, PAPP-A was not found to be a significant covariate. Nonetheless, since both parameters are useful in establishing the risk of preeclampsia, we decided to also look for any evidence of correlation. Therefore, we used a subset of our data where PAPP-A levels were matched between euploid and trisomy 21 pregnancies. We found that the difference in uterine PI was independent of the PAPP-A levels.

Many research groups have examined the importance of the uterine artery impedance to flow in screening for preeclampsia. Most studies have focused on early preeclampsia before 34–37 weeks due to its higher maternal–fetal mortality and morbidity compared to late preeclampsia. In a study with almost 120,000 normal pregnancies and 790 with preeclampsia before 37 weeks, the detection rate with uterine artery doppler at 19–24 weeks was 76% for a false positive rate of 10%. By adding the mean arterial pressure, it was possible to increase the detection rate to 81% [14]. Although the test performance of the uterine artery doppler assessment in the second trimester is good, it does not fulfil the basic prerequisites for screening due to the lack of intervention in screen positive cases.

In contrast, high risk cases after first trimester screening can be treated with Aspirin [2, 15]. Screening for preeclampsia at 11–13 weeks is based on maternal and pregnancies characteristics as well biochemical and biophysical parameters. Among the biophysical markers, uterine artery PI levels play a major role. In a meta-analysis involving more than 50,000 pregnancies, the detection rate for early preeclampsia was 48% [16]. O'Gorman et al. examined almost 36,000 pregnancies including about 1000 pregnancies with preeclampsia. The detection rate for preeclampsia before and after 37 weeks was 60% and 40% for a false positive rate of 10% if only maternal characteristics and uterine artery PI measurements are used [4]. The authors demonstrated that the additional use of the mean arterial pressure and PLGF results in a the detection rate of 75% for the same false positive rate.

In conclusion, uterine artery PI levels in the first trimester are slightly lower in pregnancies with trisomy 21. This knowledge may prove to be useful in cases where a low PAPP-A level is seen on the first trimester maternal serum biochemical evaluation to differentiate whether the more likely cause for this finding is placental dysfunction or aneuploidy, specifically trisomy 21.

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Compliance with ethical standards

Conflict of interest All authors declare that there is no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent This is a retrospective study involving ultrasound images from patients that were seen at the University of Tuebingen, Germany. All patients have agreed that clinical data can be used for retrospective studies. The study was approved by the local ethical committee. This is also stated in the Methods section (No. 350/2019BO2).

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