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# Umbilical Pulsatility Index is Associated with Fetalacidemia in Type 1 Diabetic Pregnancies

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## Abstract

This study was designed to test umbilical indices and establish a reference in pregnancies complicated by type 1 diabetes mellitus, and to correlate the pulsatility index to other clinical parameters.

We included consecutively 129 type 1 diabetic pregnant women during a five year period. During their pregnancy HbA1c, electrolytes, uric acid, diurnal blood pressure was measured and 24-h urine collected for measurement of albumin excretion rate. Umbilical blood flow measurements were done routinely from week 32 and started before week 32 on indication. Resistance and pulsatility indices and systolic-diastolic ratio were measured.

The weekly repeated measurements from gestational 32 to 34 had the lowest levels of pulsatility index in the normoalbuminuria group and highest in the micro- and macroalbuminuria group combined ($p = 0.01$).

We found an association of pulsatility index and umbilical pH ($p<0.006$). Even when adjusted for birth weight ratio, blood pressure, albumin excretion rate and HbA1c the association of pulsatility index and umbilical pH persisted ($r = -0.30$, $p = 0.016$). Glycemia expressed as HbA1c was associated with pulsatility index at nearly all measurements from week 31 to 35 and associated with albumin excretion rate.

We were not able to predict adverse feto-maternal outcome in our pregnancies using umbilical indices. The correlation of pulsatility index and HbA1c underlines the importance of glycemic status during pregnancy. Albumin excretion rate affects the level of the umbilical pulsatility index.

**Keywords:** Type 1 diabetes mellitus; Pregnancy; Pulsatility index; Umbilical cord pH; HbA1c; Albumin excretion rate

**Abbreviations:** T1DM: Type 1 Diabetes Mellitus; AER: Albumin Excretion Rate; SGA: Small-for-Gestational Age; LGA: Large-for-Gestational Age; PI: Pulsatility Index; Sys diurnal BP: Systolic diurnal Blood Pressure; Dia diurnal BP: Diastolic diurnal Blood Pressure

## Introduction

Abnomal umbilical blood flow is an indicator of fetal distress. Serial measurement is an established tool used for timing of delivery of fetuses with intrauterine growth restriction. The use of umbilical Doppler measurements in diabetic women is still debated [1]. Reference values for umbilical flow are defined according to gestational weeks in normal pregnancies with little morbidity. Even in high-risk pregnancy like those of women with type 1 diabetes mellitus (T1DM) fetal morbidity is difficult to foresee. However, in diabetic pregnancies relative large birth weight is a prominent feature even in preterm delivery [2]. Even when normoglycemia is achieved macrosomia is still a prominent feature in diabetic pregnancies [3]. Our aim was to test umbilical indices in their ability to predict adverse feto-maternal outcome, establish a reference in pregnancies complicated by T1DM, and to correlate the pulsatility index to other clinical parameters.

## Material and Methods

During five years umbilical blood indices was measured consecutively in 146 women with T1DM. Seventeen women were excluded; one was a repeated pregnancy and in the 16 other women only one umbilical measurement was performed. Thus, 129 women remained in the study. During pregnancy the women came for routine ambulatory visits every other week at which time HbA1c, electrolytes, uric acid was measured and 24-h urine collected for measurement of albumin excretion, glucose, and creatinine clearance. Albumin Excretion Rate (AER) was labellednormoalbuminuria when albumin excretion < 30 mg, microalbuminuria as 30 mg - 299 mg, and macroalbuminuria> 299 mg per 24 hours. All women were on frequent dose insulin (4-6 times daily) and glycemia was monitored by frequent home measurements using regularly calibrated home glucometers. In 92 (71%) women blood pressure was measured with a portable monitor (SpaceLab 90207, Redmond, WA, U.S.A.) using oscillometry.

Umbilical blood flow was done routinely from week 32 in T1DM and started before week 32 on indication. Resistance- and pulsatility index, and systole/diastole ratio were registered and stored as a photograph. The flow measurements were done by the associate professor in charge of the out-patient pregnant diabetes ward and, in his absence, by the registrar or consultant. Delivery was induced in week 37 to 38 if cesarean was not planned. All neonates were routinely admitted to the neonatal intensive care unit for a minimum of three days.

## Statistics

Difference between two means was tested with Student's *t*-test if Gaussian distribution was ensured; otherwise Mann-Whitney's U test was applied. Difference between two proportions was tested with Fisher's exact test if any number was less than five; otherwise $Chi^2$-test was applied. After appropriate grouping $Chi^2$-test for trend was applied in tables with more than two proportions. Repeated measures analysis of variance (two-way-ANOVA) was used for comparison

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between groups for measures taken over time from the same subject. If ANOVA was significant Newman-Keul's post-hoc test was performed to see where the groups differed. Regression analysis was performed with umbilical pH as the dependent variable. A birth weight ratio was computed by dividing the observed birth weight with the expected birth weight for the same gestational age and sex. Small-for-Gestational Age (SGA) and Large-for-Gestational / macrosomia (LGA) for the neonate of the diabetic mother were defined as a birth weight ratio of 1.0 and 1.50, respectively. The statistical software was IBM SPSS statistics 20. A two-sided p-value < 0.05 was the level of significance.

## Results

The clinical data show that duration of T1DM was longer, HbA1c, and blood pressures were higher in the group of women with macroalbuminuria (Table 1). The women with normoalbuminuria had larger babies and lower diastolic BP. Umbilical pH was < 7.00, 7.00-7.09, and 7.10 - 7.19 in one, three, and 16 neonates, respectively. SGA was found in 12 and LGA in 37 deliveries.

The umbilical Pulsatility Index (PI) was associated with AER. The weekly repeated measurements from gestational 32 to 34 had the lowest levels of PI in the normoalbuminuria group and highest in the micro- and macroalbuminuria group combined (two-way ANOVA, p = 0.01). The serial measurements of PI from week 31 to 35 showed different levels with respect to the birth weights of either SGA, AGA, and LGA; the PI levels of the SGA pregnancies were significant higher than in the AGA and LGA pregnancies (two-way ANOVA, p<0.01).

Glycemia expressed as HbA1c was associated with PI at nearly half of measurements from week 31 to 36 (Table 2 and Figure 1) and associated with AER (data not shown).

Figure 2 illustrates that the latest pre-partum measurement PI was significantly associated with pH. The PI measurements were all performed within three days of delivery. Even when adjusted for birth weight ratio, blood pressure, AER, and HbA1c the association of PI and umbilical pH persisted (r = -0.30, p = 0.016). Other vascular dysfunctions like preeclampsia, hypertension, and retinopathy were not associated with PI.

| Albumin excretion rate | Normo-albuminuria | Micro- and macroalbuminuria | All | p-values |
|---|---|---|---|---|
| No. | 107 | 22 | 129 | |
| Age (years) | 29 | 29 | 29 | 0.43* |
| Duration of T1DM (years) | 9 ± 7 | 16 ± 7 | 10 ± 8 | 0.001* |
| Parity | 1.8 | 1.6 | 1.8 | 0.22** |
| No/simple/proliferative retinopathy (no.) | 67 / 37 / 3 | 4 / 15 / 3 | 71 / 52 / 6 | 0.001# |
| HbA1c (%) | 7.2 ± 1.1 | 7.9 ± 1.2 | 7.3 ± 1.1 | 0.018** |
| Sys diurnal BP (mmHg) | 117 ± 8 | 125 ± 7 | 118 ± 9 | 0.001* |
| Dia diurnal BP (mmHg) | 70 ± 6 | 76 ± 5 | 71 ± 6 | 0.001* |
| Preeclampsia (no.) | 10 | 6 | 16 | 0.049# |
| Hypertension (no.) | 6 | 2 | 8 | 0.62§ |
| Birth weight (g) | 3820 ± 696 | 3179 ± 655 | 3711 ± 728 | 0.001* |
| Gestational age (wk) | 36.1 | 35.6 | 36.0 | 0.11** |
| Birth weight ratio | 1.37 ± 0.26 | 1.15 ± 0.19 | 1.33 ± 0.26 | 0.001* |
| Umbilical cord pH | 7.26 | 7.27 | 7.26 | 0.72** |
| PI last | 1.06 ± 0.31 | 1.21 ± 0.46 | 1.08 ± 0.34 | 0.056** |
| Sex female/ male (no.) | 59/48 | 8/14 | 67/62 | 0.15# |

*: t-test; **: Mann-Whitney U-test; #: Chi-square test; §: Fisher's exact test

**Table 1:** Clinical data of 129 pregnant women with T1DM by albumin excretionrate.

| Gestational week | PI | r | p-value |
|---|---|---|---|
| 31 | 1.15 | 0.29 | 0.006 |
| 32 | 1.13 | 0.19 | 0.058 |
| 33 | 1.09 | 0.20 | 0.057 |
| 34 | 1.14 | 0.34 | 0.001 |
| 35 | 1.06 | 0.25 | 0.026 |
| 36 | 1.11 | 0.25 | 0.082 |

r: Regression coefficient with PI as dependent and HbA1c as independent variable

**Table 2:** PI and regression coefficients of 3rd trimester HbA1c vs. PI.

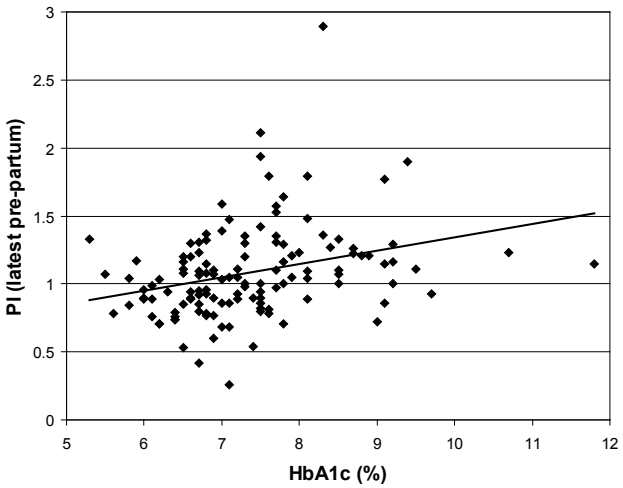


**Figure 1:** Pulsatility index measured within three days before delivery versus 3rd trimester HbA1c (r= 0.30 p<0.001, n=127).

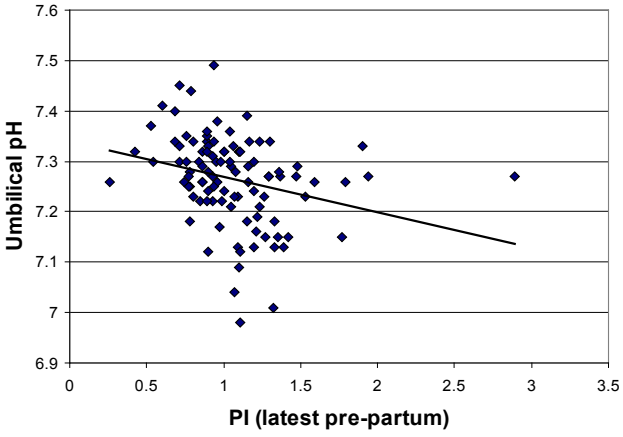


**Figure 2:** Pulsatility index measured within three days before delivery versus umbilical pH (r= -0.27, p=0.006, n=100).

The fetal outcomes were registered were neonatal hypoglycemia (n=63), neonatal hyperbilirubinemia (n=50), neonatal hypocalcemia (n=7), neonatalhyponatremia (n=1), septicemia (n=6), neonatal need for CPAP (n=20), DuchenneErb's paralysis (n=3), ventricular septum defect (n=1), atrial septum defect (n=2), multiple bone agenesis (n=1),hydrocephalus (n=1), intrauterine fetal death (n=1), and spherocytosis (n=1).However, none of these outcome alone or combined showed any association with PI; neither the malformations nor the variety of neonatal stress symptoms.

## Discussion

We find a correlation between PI of umbilical arteries and umbilical cord pH at birth. In 80 % of cases umbilical cord pH is within normal range; even though, the umbilical cord pH may be a result of the delivery. There are reports indicating that diabetic pregnancies habitually are complicated with chronic hypoxia due to hyperglycemia and hyperinsulinism as well as true malvascularization [3,4]. We corroborate this observation with a correlation between PI and maternal HbA1c.

Teramo et al. point out that maternal HbA1c correlates with fetal erythropoietin, a direct marker of intrauterine chronic hypoxia in type 1 diabetic women [3]. Conflicting reports on the value of PI in diabetic pregnancy may well stem from the fact that high and low risk populations are studied combined including gestational diabetes [2,5]. Wong et al. concluded that type 1 diabetes is the only group with sufficient risk to warrant repeat investigation [6]. Mean glycemic values are significantly higher in diabetic women with pathologic PIs suggesting that hyperglycemia causes increase in placental resistance [4]. The increase in placental resistance may be structural or functional; if the latter was true the resistance ought to decrease if the women become normoglycemic.

The conflicting reports of benefit of PI is explained by several confounding factors e.g. grouping of several gestational weeks, the timing of measurements, and mixing populations of type 1, type 2, and gestational diabetes [2,4-7]. Grunwald et al. have only 24 complete pregnancies pooled in gestational weeks 29-33 and 33-37 with random blood glucose at the times of PI measurements [2]. Whether HbA1c are present at times of PI is not clear. They find no decline of PI with increasing gestational age.

The correlation of PI and pH is logically dependent on a short interval between measurements. Wong et al. find that if the umbilical measurements are carried out within 2 weeks of delivery, they are significantly associated with adverse perinatal outcome. In their study 80% of pregnancies with elevated umbilical PI have adverse outcome if the PI is measured within one week before delivery [6]. We had an even narrower interval between measurements and delivery (≤ 3 days) because of the timed delivery in most cases; 50% were induced and 50% delivered by cesarean. We found no difference in either PI or pH with respect to delivery mode (data not shown).

The use of umbilical artery measurements in estimating prognosis in diabetic pregnancies is still controversial. We find no association with preeclampsia, hypertension or retinopathy. AER is associated with different levels of PI and, similar to our findings; Reece et al. conclude that PI may be elevated even in normoglycemic women but due to microvascular disease [7]. In their series vasculopathy was indicated by preeclampsia, hypertension, retinopathy, and microalbuminuria and had unfavorable outcome associated with PI.

When evaluating PI values for obstetrical outcome the normal birth weight ranges is skewed towards macrosomia. Teramoet el. analyzed the relationship and found the range of optimal weight of the fetus to be narrower and suggested that growth restriction is at -0.6 SD instead of 2 SD [3]. Intrauterine erythropoietin levels and birth weight show a non-linear relation and, thus, explain part of the discrepancy. Kainer et al. suggest there is an individual threshold at which maternal blood glucose causes hyperinsulinism [8]. The relation of fetal weight and intrauterine chronic hypoxia may well be U-shaped and oxidative stress markers are released into the amniotic fluid [3,9]. The relation between erythropoietin and PI is found in growth restricted fetuses of non-diabetic women [10]. Our study has too few small neonates to prove the point as the vast majority is macrosomic, and our conclusion hold mainly for this condition.

## Conclusion

We find a correlation of the pulsatility index to pH and AER in T1DM women. We are not able to predict adverse feto-maternal outcome in our series of mainly macrosomic neonates. The correlation of pulsatility index and other clinical parameters suggests that a larger study is relevant including SGA neonates.

### References

1. Alfirevic Z, Stampalija T, Gyte GM (2010) Fetal and umbilical Doppler ultrasound in high-risk pregnancies. Cochrane Database Syst Rev.
2. Grunewald C, Divon M, Lunell NO (1996) Doppler velocimetry in last trimester pregnancy complicated by insulin-dependent diabeste mellitus. Acta Obstet Gynecol Scand 75: 804-808.
3. Teramo KA, Widness JA (2009) Increased fetal plasma and amniotic fluid erythropoietin concentrations: markers of intrauterine hypoxia. Neonatology 95: 105-116.
4. Fadda GM, Cherchi PL, D'Antona D, Ambrosini G, Marchesoni D, et al. (2001) Umbilical Artery Pulsatility Index in Pregnancies Complicated by insulin-Dependent Diabetes mellitus without Hypertension. GynecolObstet Invest 51: 173-177.
5. Bracero LA, Schulman H (1991) Doppler studies of the uteroplacental circulation in pregnancies complicated by diabetes.Ultrasound Obstet Gynecol 1: 391-394.
6. Wong SF, Chan FY, Cincotta RB, Mcintyre DH, Stone M (2003) Use of umbilical artery Doppler velocimetry in the monitoring of pregnancy in women with pre-existing diabetes. Aust N Z J Obstet Gynecol 43: 302-306.
7. Reece EA, Homko CJ, Wiznitzer A (1994) Doppler velocimetry and the assessment of fetal well-being in normal and diabetic pregnancies. Ultrsound Obstet Gynecol 4: 508-514.
8. Kainer F, Weiss PA, Huttner U, Haas J, Reles M (1997) Levels of amniotic fluid insulin and profiles of maternal blood glucose in pregnant women with diabetes type-I. Early Hum Dev 49: 97-105.
9. Escobar J, Teramo K, Stefanovic V, Andersson S, Asensi MA, Arduini A, et al. (2013) Amniotic Fluid Oxidative and Nitrosative Stress Biomarkers Correlate with Fetal Chronic Hypoxia in Diabetic Pregnancies. Neonatology 103:193-198.
10. Girsen A, Makikallio K, Hiilesmaa V, Hamalainen E, Teramo K, Rasanen J. (2007) The relationship between human fetal cardiovascular hemodynamics and serum erythropoietin levels in growth-restricted fetuses. Am J ObstetGynecol 196; 467.e1-e6.