Diplomarbeit

The Placenta in Women with Type 1 Diabetes Mellitus in Consideration of the Maternal HbA1c - A Literature Review

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Graz, am 13.02.2019 *Sarah Spiekermann eh.*

Danksagung

Der größte Dank gilt ao.Univ.-Prof. Dr.phil. Gernot Desoye für die Bereitstellung des spannenden Themas, sowie der umfassenden Betreuung während der Erstellung der Diplomarbeit. Seine Arbeit in der Forschung und Lehre sind für mich eine Inspiration für meinen eigenen Weg in der Medizin.

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1 Zusammenfassung

Einleitung: Die menschliche Plazenta ist ein transientes Organ, welches die adäquate Versorgung des Fetus gewährleistet. Die strukturelle Entwicklung und Funktion kann durch maternale oder fetale Erkrankungen gestört sein. Schwangerschaften, die durch mütterlichen Typ 1 Diabetes Mellitus (T1DM) beeinflusst werden sind, im Vergleich zu Typ 2 Diabetes Mellitus (T2DM) oder Gestationsdiabetes (GDM), selten. Aus diesem Grund haben Untersuchungen des Einflusses des T1DM auf die Plazenta einen geringeren Stellenwert in der Forschung. Die vorliegende Arbeit untersucht die plazentaren Veränderungen bei T1DM, unter besonderer Berücksichtigung der maternalen Glukoseeinstellung, definiert durch den Glykohämoglobin A-Wert (HbA1c).

Methoden: Für die vorliegende Arbeit wurde eine umfassende Literaturrecherche mit der Onlinedatenbank ‚PUBMED' durchgeführt. Die Zusammenfassungen wurden auf ihre Relevanz in Hinblick auf die Untersuchung von T1DM und Plazenta geprüft. Anschließend wurden die Arbeiten vollständig analysiert und anhand der HbA1c-Werte kategorisiert. Ein exzellent eingestellter T1DM wurde definiert als HbA1c ≤6%, ein gut eingestellter als 6.1-7% und eine nicht optimale Glukosekontrolle als HbA1c >7%. Es wurde der Einfluss des Durchschnittswertes in der Schwangerschaft sowie der Einfluss zu bestimmten Zeitpunkten untersucht. Die Nebenziele der Arbeit waren die Darstellung der Entwicklung des Plazentagewichtes für den Zeitraum zwischen 1960 und 2017, der Einfluss des fetalen Geschlechts auf die Plazenta sowie die Entstehung oxidativen und nitrosativen Stresses in der Plazenta.

Ergebnisse: Die häufigsten plazentaren Veränderungen bei T1DM sind erhöhtes Plazentagewicht, Zottenunreife sowie strukturelle vaskuläre Veränderungen. Diese zeigen sich auch in Plazenten von Müttern mit exzellent eingestelltem (≤6%) T1DM. Der Einfluss des HbA1c-Wertes auf die Plazenta zu bestimmten Zeitpunkten der Schwangerschaft ist in der aktuellen Studienlage nicht eindeutig zuzuordnen. Jedoch ist der aus den Studien errechnete Durchschnittswert des HbA1c mit 7,3% im ersten Trimester, im Vergleich zum zweiten (6,3%) und dritten (6,4%) Trimester deutlich erhöht. Das Plazentagewicht fluktuierte für den untersuchten Zeitraum zwischen 1960 und 2017. Mit 637g war für die Dekade zwischen 2001 und 2010 der höchste Durchschnittswert zu verzeichnen. Das männliche fetale Geschlecht ist ein Risikofaktor für die Entstehung histopathologischer

Veränderungen der Plazenta bei Gesunden und T1DM. Des Weiteren verursacht maternaler T1DM oxidativen und nitrosativen Stress in der Plazenta.

Konklusion: Die Ergebnisse zeigen, dass auch ein exzellent eingestellter T1DM zu plazentaren histopathologischen Veränderungen führen kann. Trotz der unsicheren Studienlage kann vermutet werden, dass der mütterliche HbA1c im ersten Trimester einen größeren Einfluss auf die Plazenta hat, als im zweiten oder dritten Trimester. Die Korrelation zwischen dem präkonzeptionellen HbA1c-Wert und Plazentaveränderung bei T1DM wurde bisher nicht untersucht. Für die Untersuchung dieses Zusammenhangs sind Studien notwendig. Plazentarer oxidativer und nitrosativer Stress könnte der zugrundeliegende Mechanismus für die strukturellen Gefäßveränderungen sein.

2 Abstract

Introduction: The human placenta is a transient organ aiming at an adequate and healthy fetal development. Its complex formation und function can be affected by maternal or fetal diseases. Pregnancies complicated by Maternal Type 1 Diabetes Mellitus (T1DM) are rarer than Type 2 Diabetes Mellitus (T2DM) or Gestational Diabetes Mellitus (GDM). Thus, investigations with respect to the placental alterations in T1DM have less emphasis in research. The present work analyses the impact of T1DM on the placenta in consideration of the maternal glycemic control, reflected by the glycated hemoglobin A (HbA1c).

Methods: A comprehensive literature review was conducted. The online database 'PUBMED' was utilized for this research. Abstracts were reviewed for the sole investigation of T1DM placentas. Then results of full-text articles were reviewed and categorized after the maternal HbA1c value during pregnancy. An excellent glycemic control was defined as a HbA1c value ≤6%, a good control as 6.1-7% and a non-optimal glycemic control as values >7%. Secondary objectives were a representation of the development of placental weight for the time period between 1960 and 2017, the effect of the fetal sex on the placenta as well as the emergence of placental oxidative and nitrative stress.

Results: The most frequent placental abnormalities in T1DM are an increased placental weight, villous immaturity and structural vascular changes, even in excellent controlled (≤6%) T1DM. Regarding the impact of the maternal HbA1c at a specific time period during pregnancy, studies show inconclusive results. Nevertheless, the average calculated HbA1c

value is increased in the first trimester with 7.3% compared to 6.3% in the second and 6.4% in the third trimester. The placental weight fluctuated in the time period between 1960 and 2017. The highest average value was 637g for the decade between 2001 and 2010. The male fetal sex is a risk factor for placental histopathologic changes in healthy and T1DM pregnancies. In addition, placental oxidative and nitrative stress emerge in T1DM.

Conclusion: The results show that even well controlled T1DM can lead to placental abnormalities. Although the results regarding the association between the maternal HbA1c at a specific time period and placental changes are inconsistent, it can be suggested that the first trimester HbA1c has a greater impact than the second or third trimester HbA1c. The correlation of pre-conceptional HbA1c value and placental abnormalities in T1DM has not been investigated yet. Therefore, further studies are needed to investigate a possible correlation. Placental oxidative and nitrative stress seems to be the underlying cause leading to structural vascular alterations.

3.1 Abbreviations

AFD ..... *Appropriate for date*
AGE ..... *Advanced glycation products*
BMI ..... *Body Mass Index*
CBM ..... *Capillary basement membrane*
CRP ..... *C-reactive protein*
ECM ..... *Extracellular matrix*
eNOS ..... *endothelial nitric oxide synthase*
ETC ..... *Electron transport chain*
Ets-1 ..... *E26 transformation specific oncogene homolog 1*
FGF ..... *Fibroblast growth factor*
Flt-1 ..... *Fms related tyrosine kinase 1*
GDM ..... *Gestational Diabetes Mellitus*
GLP-1 ..... *Glucagon-like peptide 1*
GPx ..... *Glutathione peroxidase*
GR ..... *Glutathione reductase*
GRB10 ..... *Growth receptor binding protein 10*
GSH ..... *Reduced glutathione*
H_2O_2 ..... *Hydrogen peroxidase*
HbA1c ..... *Glycated hemoglobin*
HFD ..... *Heavy for date*
HIF-1 ..... *Hypoxia inducible factor 1*
HO· ..... *Hydroxyl radical*
HO-1 ..... *Heme oxygenase 1*
IDDM ..... *Insulindependent Diabetes Mellitus*
IGF ..... *Insulin-like growth factor*
IGF1R ..... *Insulin-like factor 1 receptor*
IL-6 ..... *Interleukin-6*
IPC ..... *Index of Placental Changes*
IR ..... *Insulin receptor*
IUGR ..... *Intrauterine growth restriction, Intrauterine growth restriction*
KDR ..... *Kinase insert domain receptor*
KLF-8 ..... *Krüppel-like factor 8*
LDL ..... *Low-density lipoprotein*
LGA ..... *Large for gestational age*
LPO ..... *Lipid peroxidase*
MDA ..... *Malondialdehyde*
MMP ..... *Matrix metalloproteinase*
MODD ..... *Mean of daily difference in blood glucose values*
NAMPT ..... *Nicotinamide phosphoribosyltransferase*
NF-κB ..... *Nuclear factor kappa-light-chain-enhancer of activated B*
NICU ..... *Neonatal intensive care unit*
Nrf 2 ..... *NF-E2-related factor 2*
NT ..... *Nitrotyrosine*
$O\cdot_2^-$ ..... *Superoxide anion radical*
PBEF ..... *pre-B cell colony enhancing factor*
PCI ..... *Placental Changes Index*
PGDM ..... *Pregestational Diabetes Mellitus*

PGE2 ..... *Prostaglandin E2*
PGH..... *Placental growth hormone*
PIGF ..... *Placental growth factor*
PW/BW ..... *Placental weight/ birth weight*
RC..... *Redundant connections*
ROS ..... *Reactive oxygen species*
SFD..... *Small for date*
SGA..... *Small for gestational age*
SOD..... *Superoxid-Dismutase*
STAT-3..... *signal transducer and activator of transcription 3*
T1DM ..... *Type 1 Diabetes Mellitus*
T2DM ..... *Type 2 Diabetes Mellitus*
TAOC ..... *Total antioxidant capacity*
TBARS ..... *Thiobarbituric acid reactive substances*
TBM ..... *Trophoblast basement membrane*
TIMP-2 ..... *tissue inhibitors of metalloproteinase-2*
TNFα ..... *Tumor necrosis factor alpha*
uNK cells..... *Uterine natural killer cells*
VEGF ..... *Vascular endothelial growth factor*
VEGFR..... *Vascular endothelial factor receptor*

3.2 List of Tables and Figures

4 Introduction

T1DM characterized by an absolute insulin deficiency. It is caused by an autoimmune destruction of pancreatic beta cells in the islets of Langerhans. The underlying cause remains still unknown, but it is assumed that its etiology is multifactorial (1). Pregnant women with T1DM are known to have higher rates of fetal or maternal complications. T1DM women have higher incidences for preeclampsia, pregnancy-induced hypertension, preterm delivery or caesarian section (2–7). Impaired outcomes can be aggravated by maternal overweight or vascular diseases (4, 8). Neonates from T1DM mother have a greater risk for stillbirth, congenital malformations like congenital heart diseases or renal malformations, perinatal mortality and neonatal morbidity. Large for gestational age (LGA) infants, macrosomia or infants with a greater fat mass occur more frequently in T1DM. They have increased incidences of hypoglycemia and jaundice at birth and decreased APGAR scores at 1 and 5 minutes (3, 5, 6, 9–15). Macrosomic infants have a higher risk to become overweight in childhood (16). Thus, T1DM pregnant women belong to a high-risk group during pregnancy. The current German guidelines recommend a good glycemic control at least three months prior to conception (17). The target range would be a glycated hemoglobin A (HbA1c) value <7% or preferable <6.5%. The measurement should be repeated every 4 to 6 weeks. Additionally, self-measurement for fasting, post-prandial or mean daily glucose levels are advisable (17).

The human placenta is one of the most important organs, although it only exists for nine months. It is responsible for the right supply to enable a healthy fetal development. It is a highly complex organ that takes over number of tasks. It is responsible for the gas exchange and nutrient transfer between mother and fetus with different transport mechanisms. It functions as an endocrine organ and can transfer immunity from the mother to the fetus. Thus, it is not only a passive conduit but can adapt to several circumstances by influencing maternal blood flow or metabolism or it can adapt structurally to always ensure an adequate supply for the fetus (18, 19). This may suggest that the human placenta in T1DM adapts to the hyperglycemic environment as well. The question is, how the placental structure adjusts to it and to what extent the maternal HbA1c correlates with the extent of placental alterations in T1DM.

5 Aims

Pregnant women suffering from T1DM are less uncommon than type 2 diabetes mellitus (T2DM) or gestational diabetes mellitus (GDM). Therefore, investigations with respect to the placental alterations in T1DM have less emphasis in research. Thus, the aim of this work is to give an overview about the current known literature and analyze the results regarding its meaning for the medical support prior to and during pregnancy.

The primary focus of this work are the histopathologic changes in relation to maternal glucose control, defined by maternal HbA1c levels during pregnancy. The correlation between the average HbA1c and placental alterations as well as the correlation between the first, second and third trimester HbA1c and the placenta is investigated in this work. The latter analyses shall help identify the most critical period in pregnancy, in which poor glycemic control has the most pronounced effect on the placenta. Since the quality of glycemic control has improved over the past decades, potential changes in placental development, using placental weight as proxy, is analyzed. Additionally, the effect of the fetal sex on the placental structure and at least molecular mechanisms, like oxidative stress and inflammation, appearing in pregnancies affected by T1DM, are taken into consideration.

The elaboration of the effects of T1DM on the morphology and function of the placenta are investigated by the analysis of different studies dealing with T1DM in pregnancy and the comparison of these results in view of its clinical importance.

6 Methods

The analysis of the present work is based on published literature investigating the effect of maternal T1DM on the human placenta. The online database 'PUBMED' was the main source for the primary literature. To expand the results of primary research, references mentioned by the literature found on 'PUBMED' were used as a second source of information and hence defined as secondary literature. A time range between 1960 until September 2018 was used for this research.

The first aim was to get an overview about published papers dealing with the topic of maternal T1DM in its impact on the placenta. Therefore, the keywords *'Type 1 diabetes mellitus AND placenta'* were searched on 'PUBMED'. Regarding to these keywords, 202 results were displayed, the first published in 1970. The abstracts were analyzed and sorted regarding the determined exclusion and inclusion criteria mentioned in Table 1. Finally, 39 studies remained. This number of studies was supplemented by secondary literature.

Table 1 The exclusion and inclusion criteria relating to the searched keywords 'type 1 diabetes mellitus AND placenta'

Exclusion Criteria	*Inclusion Criteria*
• Non-human placentas • Analysis of maternal serum markers (except maternal HbA1c value) • Effects of maternal T1DM on the Fetus • GDM, T2DM	• Human T1DM placentas • Comparisons between T1DM and T2DM or GDM

HbA1c= glycated hemoglobin A, T1DM= type 1 diabetes mellitus, GDM= gestational diabetes mellitus, T2DM= type 2 diabetes melitus

6.1 Comprehensive Research on the Maternal HbA1c Value and the Placenta

After the first review of studies investigating the human placenta in T1DM, a more detailed research on 'PUBMED' followed. The reason was to narrow down and specify the results. The main research issue, the effect of the average HbA1c value during pregnancy as well as first second and third trimester HbA1c, was evaluated by the search terms shown in table 2.

Different time ranges and search terms were used to extend the number of results. The papers were classified by the maternal HbA1c during pregnancy to point out differences and similarities in placental pathologies depending on maternal glycemic control. Some studies mentioned the HbA1c measured during the different trimesters. These were analyzed concerning the importance of the HbA1c at different time points during gestation. The perinatal outcome in relation to maternal glycemic control was supplemented to support the results.

Table 2 The searched terms used for the investigation of the maternal glucose control and its impact on the placenta

Search term	*Results 1960-1980*	*Results 1981-2018*
HbA1c AND placenta	0	78
Glucose control AND placenta	42	586

HbA1c= glycated hemoglobin A

6.2 Comprehensive Research on the Development of Placental Weight in T1DM

Furthermore, one aspect of this work is the development of maternal glycemic control during pregnancy demonstrated by the development of placental weight from 1960 till 2017. Table 3 shows the terms that were utilized for this research. Studies published between 1960 and December 2017 were included. To outline the development of the placental weight for specific time periods, the search was divided into two different time ranges. The use of two different search terms was necessary because the keywords 'Placental weight AND type 1 diabetes mellitus' yielded only two results in the time range from 1960 to 1980 and none of them was useful for this work. Table 3 also displays the number of studies that remained after exclusion. All studies which analyzed other diabetes types than T1DM, pregestational diabetes mellitus (PGDM) or insulin dependent diabetes mellitus (IDDM), were excluded. One exception was made for a study published in 1964. The diabetes was unclassified but T2DM was more uncommon in these years. Hence, it was included in this work. Additionally, only *in vivo* trials were included. Although this part of research took place after the research for the role of maternal HbA1c, it is mentioned in the first section of the results.

The reason is to maintain a logic presentation of the results commencing with the macroscopic alterations.

Table 3 The search terms used for the analysis of the placental weight development over the last five decades and their results found on 'pubmed'

Search term	*Results 1960-1980*	*Results 1981-2017*
Placental weight AND type 1 diabetes	2	118
Placental weight AND diabetes	67	1075
After exclusion	4	6

Exclusion criteria: T2DM, GDM, studies with unclassified diabetes, *in vitro* trials

The tables and figures in this work which include calculated mean values from different studies have been calculated as follows: the mean value quoted by a study was multiplied with the number of investigated cases; these results were added up and finally divided by the summed numbers of cases from all studies included in the calculation. The statistic programs SPSS and Excel were used to support these calculations.

6.3 Additional Search Terms

In addition, further search terms were used to narrow down the number of results and specify the results regarding the different issues of this work. These search terms and the number of results is displayed in table 4.

Table 4 Additional search terms used to narrow down results

Search terms	*Number of results*
Placental weight AND type 1 diabetes AND HbA1c	32
Insulin AND type 1 diabetes AND placenta	100
VEGF AND type 1 diabetes AND placenta	5

"Diabetes Mellitus, Type 1"[Mesh]) AND "Angiogenesis Modulating Agents"[Mesh]) AND "Glycated Hemoglobin A"[Mesh]	4
IGF AND type 1 diabetes AND placenta	14
placental oxidative stress AND type 1 diabetes	16
Oxidative stress AND placenta AND hba1c	4
Inflammation AND placenta AND hba1c	1

VEGF= vascular endothelial growth factor, IGF= insulin-like growth factor, HbA1c= glycated hemoglobin A

7 Results

7.1 Placental Weight and Perinatal Outcome

The placenta is a transient organ, responsible for the nutrient supply for the fetus during pregnancy. It builds the connection between mother and fetus. Placental alterations, caused by maternal diseases or fetal conditions, have an impact either on the gravida, the fetus, or both.

It is known, that there is a linear relationship between placental weight and birth weight, illustrated by the PW/BW ratio. It was shown that a high PW/BW ratio is associated with diseases in adult life, for example a higher risk of hypertension (20) or an increased cardiovascular disease mortality (21). Additionally, a high PW/BW ratio is not just associated with an increased risk for diseases in adult life, but also with complications during pregnancy and the perinatal period. The perinatal outcome includes perinatal mortality at a gestational age >22 weeks until 28 days after birth, preterm birth <37 weeks, major congenital malformations as well as small for gestational age (<10th percentile) or large for gestational age (>90th percentile) neonates (22). A high first and second trimester placental volume as well as placental quotient (placental volume/gestational age) were associated with an increased risk for macrosomia and LGA infants (23, 24).

A recent published study by Matsuda et al. (2018) (25) examined 93.034 placentas and infants from vaginally born singleton deliveries. The aim was to investigate the rate of perinatal death among small for date (SFD), appropriate for date (AFD) and heavy for date (HFD) group. SFD was defined as a birth weight and neonatal height less than the 10th percentile. AFD between the 10th and 90th percentile and HFD over the 90th percentile. The

AFD group had the highest rates of a balanced placental and infant growth. The cases with a balanced growth showed the lowest rate of perinatal death.

Further, Shehata et al. (2011) (26) observed more frequent admissions to the NICU, apgar scores <7 at five minutes in infants with a high PW/BW ratio than in those with a low PW/BW ratio. Breech presentation and caesarean section were also more common in the high PW/BW ratio group. In the group with a high PW/BW ratio 9.6% of the women had DM, compared to 3.39% in the low PW/BW ratio group and 5.3% in the normal PW/BW ratio group (p<0.0001).

7.2 PW/BW Ratio and the Role of Maternal HbA1c in T1DM

Table 5 demonstrates the placental weight percentiles depending on the gestational age and fetal sex. This illustration was developed by Almog et al. (2011) (27) and is supposed to ensure a better comparability between the placental weight of healthy women and T1DM women in this work. Figure 1 is graphical presentation of the 3rd, 50th and 97th placental weight percentile in boys and girls at the gestational age of 40 weeks. The values are extracted from Table 5. It demonstrates a wide range between the 3rd and 97th percentile with a difference of more than 500g in boys and girls from healthy gravidae.

Table 5 Placenta weight percentile curves for healthy singleton deliveries in girls and in boys, extracted from Almog et al. (2011) (27)

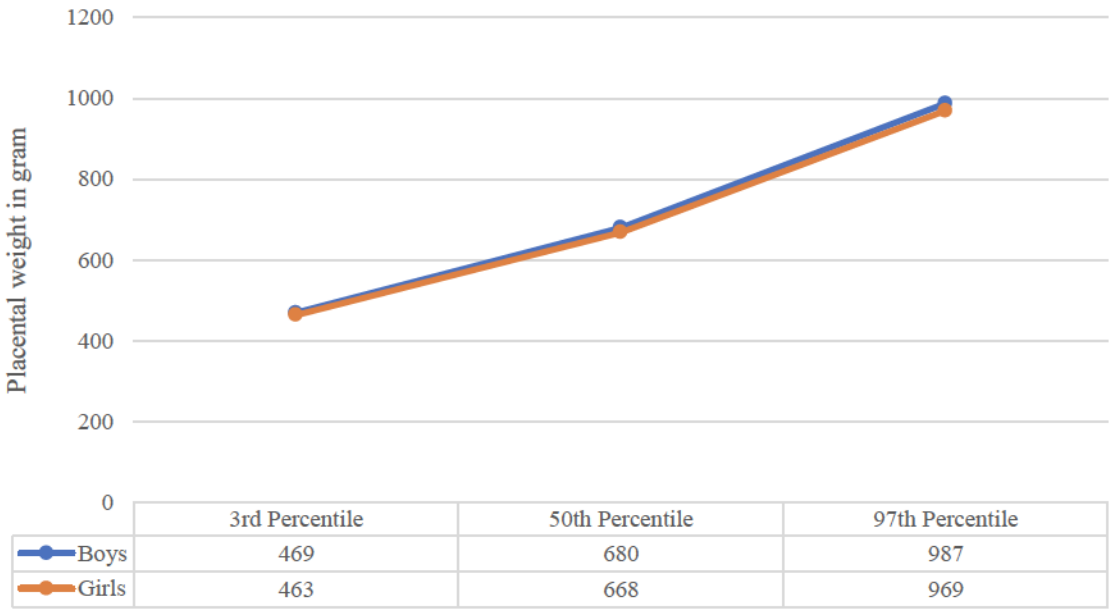
The 3rd, 10th, 25th, 50th, 75th, 90th, and 97th percentiles of placental weight by gestational age for girls' deliveries.

GestAge	#	3rd	10th	25th	50th	75th	90th	97th
24	5	134.1	161.7	195.7	242.3	300.7	365.9	444.7
25	4	153.0	183.6	221.2	272.6	336.6	407.5	493.0
26	9	171.8	205.3	246.2	301.8	370.7	446.7	537.9
27	16	190.1	226.2	270.1	329.4	402.5	482.7	578.4
28	14	208.4	246.8	293.4	356.1	432.8	516.6	616.1
29	17	227.5	268.3	317.5	383.3	463.5	550.7	653.6
30	12	248.3	291.6	343.4	412.5	496.3	586.8	693.3
31	21	271.3	317.1	371.9	444.4	531.9	626.0	736.0
32	34	295.9	344.4	402.0	478.0	569.0	666.5	780.0
33	48	321.2	372.2	432.5	511.6	606.0	706.4	822.7
34	57	346.6	399.9	462.5	544.3	641.4	744.2	862.6
35	114	370.7	425.7	490.2	573.9	672.7	776.8	896.1
36	186	393.0	449.3	515.0	599.9	699.5	803.9	923.1
37	477	413.3	470.4	536.7	622.0	721.4	825.2	943.0
38	1370	431.8	489.3	555.7	640.7	739.3	841.7	957.2
39	2606	447.7	505.0	571.0	654.9	751.8	851.8	964.1
40	2714	463.2	520.2	585.4	668.0	762.8	860.2	969.1
41	1820	478.8	535.3	599.7	680.8	773.4	868.1	973.4
42	355	490.9	546.4	609.3	688.2	777.8	868.8	969.6
43	33	499.6	553.7	614.6	690.6	776.5	863.4	959.1
44	5	507.1	559.5	618.2	691.2	773.1	855.5	945.9

The 3rd, 10th, 25th, 50th, 75th, 90th, and 97th percentiles of placental weight by gestational age for boys' deliveries.

GestAge	#	3rd	10th	25th	50th	75th	90th	97th
24	9	164.7	199.6	242.7	301.7	375.1	456.6	554.5
25	10	176.8	213.3	258.1	319.1	394.7	478.1	577.8
26	11	188.9	226.9	273.3	336.1	413.5	498.5	599.7
27	19	201.6	241.0	288.8	353.3	432.4	518.7	621.0
28	17	215.0	255.9	305.2	371.4	452.1	539.8	643.2
29	16	230.4	272.8	323.9	392.0	474.7	564.0	668.9
30	15	248.7	293.1	346.3	417.0	502.2	593.9	700.9
31	27	270.0	316.8	372.6	446.2	534.6	629.1	739.0
32	49	293.4	342.6	401.0	477.7	569.3	666.8	779.5
33	39	318.1	369.7	430.6	510.3	604.9	705.1	820.4
34	87	343.4	397.3	460.6	543.0	640.2	742.7	860.1
35	147	368.3	424.1	489.4	573.9	673.1	777.1	895.7
36	250	392.1	449.4	516.2	602.1	702.5	807.3	926.1
37	524	414.8	473.3	541.0	627.8	728.7	833.4	951.7
38	1435	434.9	493.9	562.0	648.8	749.2	852.9	969.4
39	2597	452.1	511.2	578.9	664.9	763.8	865.5	979.3
40	2798	468.9	527.7	595.0	679.9	777.0	876.4	987.1
41	1888	486.5	545.2	611.8	695.6	791.0	888.0	995.6
42	414	501.6	559.5	625.1	707.1	799.9	894.0	997.8
43	36	515.0	571.9	636.0	715.8	805.7	896.3	995.9
44	2	528.5	584.3	646.9	724.3	811.2	898.3	993.6

Figure 1 The 3rd, 50th and 97th percentile of placental weight at gestational week 40 in male and female infants from healthy women. The values are extracted from Almog et al. (2011) (27).



	3rd Percentile	50th Percentile	97th Percentile
Boys	469	680	987
Girls	463	668	969

The placental weight at 40 weeks of gestation in male and femlae infants

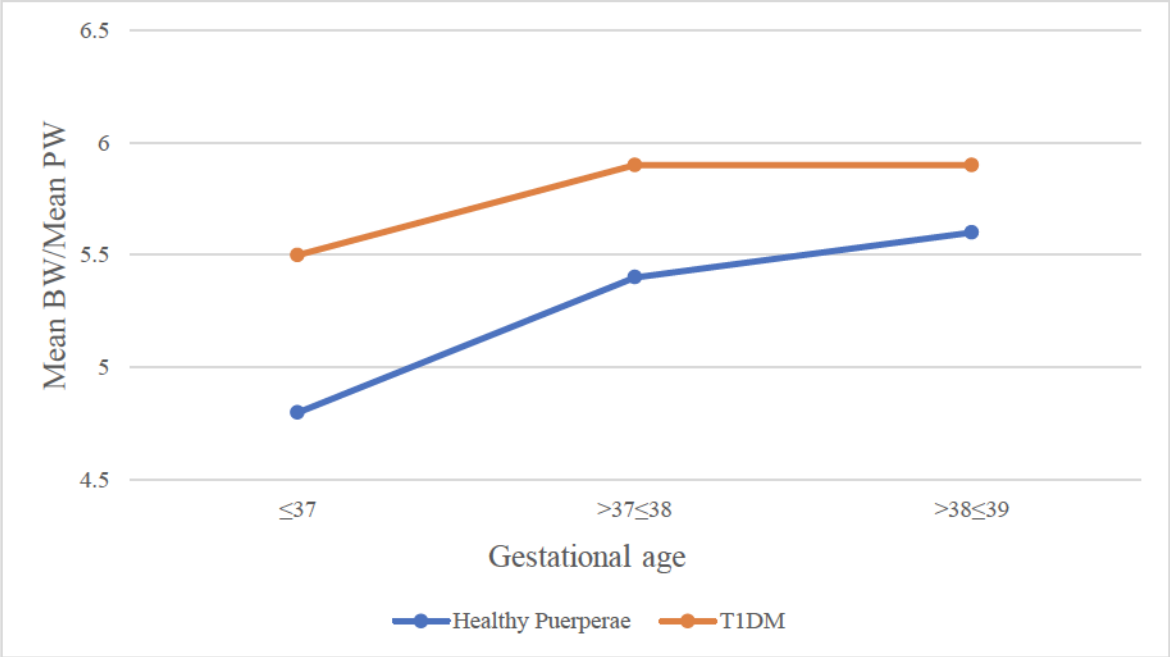
The placental weight and birth weight in women with T1DM in general are significantly higher than in normal pregnancies. T1DM further increases the risk for LGA infants (28–31). Strom-Roum et al. (2013) (30) analyzed all singleton deliveries between 1999 and 2008 (n= 536 997). They measured a mean placental weight of 736.6g with a mean gestational week of 38.2 in diabetic pregnancies (T1DM, T2DM, GDM) compared to 672.1g and 39.4 weeks in the non-diabetic group. In comparison to the placental weight percentiles shown in Table 5, the placental weight in the diabetic group corresponds approximate to the 75th percentile in both fetal sexes compared to the non-diabetic group which conforms more to the 50th percentile.

Furthermore, the placental weight positively correlated with the incidence of LGA neonates (32). Besides the birthweight, the placental weight correlated with morphologic alterations. Nelson et al. (2009) (33) found a strong correlation between placental weight and villous volume, intervillous space volume and nonparenchymal volume. The placental weight was not mentioned for both sexes separately.

Additionally, an association between maternal glycemic control and placental and birth weight was observed (34). Especially a poor glycemic control (HbA1c ≥8.5%) in the first trimester, but not in the second or third trimester, significantly correlated with placental

weight (32). Both studies did not differentiate the placental weight for male and female neonates.

Figure 2 Mean birth weight/mean placental weight ratio in relation to gestational age in healthy puerperae and in puerperae with preexisting diabetes T1DM. The calculated values are extracted from Gloria-Bottini et al. (2016) (29)



T1DM= type 1 diabetes mellitus

Figure 2 demonstrates the mean BW/PW ratio in a group with preexisting T1DM compared to a healthy group (29). It shows that the BW/PW ratio is increasing towards the last weeks of gestation in both groups but the gap between the two groups is the highest at a gestational age ≤37 weeks, with a higher BW/PW ratio in the T1DM group. Therefore, the increase of the BW/PW ratio towards the end of gestation is less in the T1DM group.

7.3 The Development of Placental Weight in T1DM from 1960 till 2017

The previous paragraph points out the difference of placental weight between T1DM and healthy gravidas by recently published papers. The treatment of T1DM has changed over the years and new medications were developed. Johnstone et al. (2006) (35) observed a reduction of perinatal mortality between 1960 and 1999. Further, maternal weight increased significantly, as well as the neonates birth weight and gestational week at delivery (p<0.001), but the standardized birth weight did not change significantly over the years (p=0.23).

The changes in treatment of T1DM and the development of perinatal outcome indicate that the placental weight changed over the years as well. In Table 6 a total number of 18 studies are listed. All investigated the placental weight in women with T1DM or PGDM. The oldest paper found was published in year 1964. Additional data like the mean gestational week at delivery, as well as the glycemic control during pregnancy are added in the table as well.

Finally, the available data were averaged for ten-year intervals to graphically determine a potential trend. The course of the placental weight is shown in Figure 3. Intervals of ten years were necessary because there were no data for each year.

Table 6 The development of placental weight in T1DM from 1960 till 2017

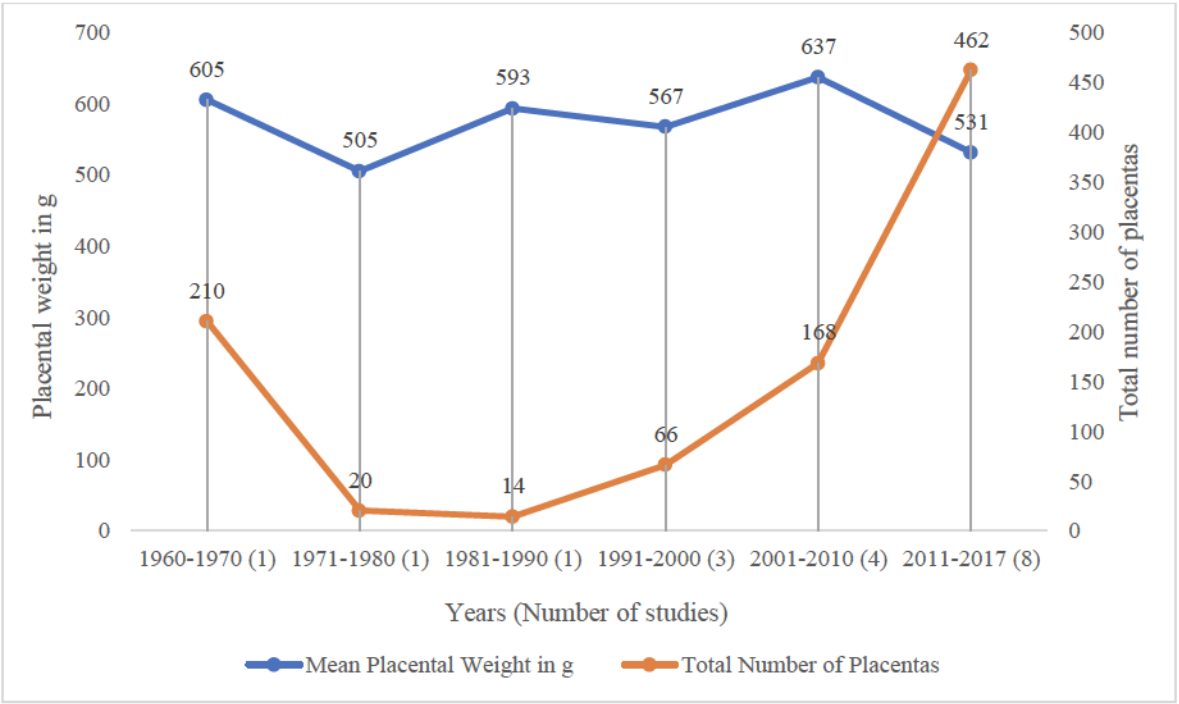
Year (Reference)	**Mean Gestational Week at Delivery (SD)**	**Average Glycemic Control During Pregnancy or HbA1c in % (SD)**	**Mean Placental Weight in gram (Diabetes Type)**	**Total Number of Subjects**
1964 (36)	-	-	472 (Unclassified) 470 540 621 666 766 842 680	4 (birthweight <2000g) 20 (2100-2500g) 60 (2501-3000g) 78 (3001-3500g) 48 (3501-4000g) 23 (4001-4500g) 6 (4501-5000g) 1 (>5000g)
1975 (37)	Until 34 Until 36 Until 38 Until 40	-	476.25 (White B, C, D/E/F) 563 (White C) 517.17 (White B, C, D/E/F) 295 (White B)	4 3 12 1
1987 (38, 39)	36.05 (33-39)	7.4 (0.98)	552 (IDDM) 593 (IDDM)	18 14 of the 18 (from pregnancies of 36 to 41 weeks)
1993 (40)	37.0	7 (4.6-9.7)	585 (White D)	11
1994 (41)	38. 7 (0.23) 37.1 (0.09)	Class B: 6.1 (4.4-9.2) Class C: 6.4 (4.7-8.9) Class D: 6.8 (4.6-9.7)	572 (White Class ABC) 560 (White Class DFR)	39 16

		Class F/R: 6.8 (5.5-12.0)		
2003 (42)	(AGA: 264 days, n=34 LGA: 257 days, n=24)	6.3 (0.9)	560 (T1DM)	58
2005 (43)	39-42	Well controlled	639.8 (PGDM)	10
2006 (44)	37.6 (37-41)	-	613 (T1DM)	12
2009 (33)	37.8 (±1.4)	5-12 weeks: 7.8 (1.2) 16-24 weeks: 6.8 (0.9) 26-34 weeks: 7.0 (1.0) 35-40 weeks: 6.7 (1.0)	690 (T1DM)	88
2011 (45)	268 days (±5)	7.8 (0.9)	576 (T1DM)	10
2012 (46)	38.12 (35-40)	4.7 (1.2)	574 (T1DM)	17
2012 (47)	37.0 (3.74)	1st Trimester: 7.4 (1.4) 2nd Trimester: 6.4 (1.0) 3rd Trimester: 6.5 (1.0)	486 T1DM)	53
2012 (48)	38	Early Pregnancy: 7.4 (1.3) 14 weeks: 6.4 (0.7) 20 weeks: 6.1 (0.7) 36 weeks: 6.2 (0.8)	513 (PGDM)	74
2014 (49)	37 (36-38)	8.3 (7.2-9.6)	490 (T1DM)	117
2015 (50)	37.5 (2.1)	1st Trimester: 7.4 (1.5) 2nd Trimester: 6.4 (0.8) 3rd Trimester: 6.4 (0.8)	499.6 (T1DM)	27
2016 (51)	38.3 (1.2)	4.7 (1.3)	590 (T1DM)	16
2016 (29)	≤ 37 >37-≤38 >38-≤39 >39	137,61 mg/dl	566 (T1DM) 598 619 650	81 38 27 2
2016 (32)	35.2 (3.7)	1st Trimester: 9.7 (1.9), 2nd Trimester:	<500 (T1DM)	71

		8.0 (1.3), 3rd Trimester: 7.9 (1.2)		
	36.5 (2.00)	1st Trimester: 9.7 (1.9), 2nd Trimester: 8.2 (1.6), 3rd Trimester: 8.0 (1.4)	500 to <628	79
	37.3 (1.7)	1st Trimester: 9.3 (1.8), 2nd Trimester: 7.9 (1.5), 3rd Trimester: 7.6 (1.1)	628 to <736	76
	37.3 (1.6)	1st Trimester: 8.9 (1.8), 2nd Trimester: 7.6 (1.3), 3rd Trimester: 7.6 (1.6)	>736	76

SD= standard deviation, HbA1c= glycated hemoglobin A, T1DM= type 1 diabetes mellitus, PGDM= pregestational diabetes mellitus, AGA= average for gestational age, LGA= large for gestational age

Figure 3 Mean placental weight and total number of placentas in T1DM gravidae from 1960 till 2017 in intervals of ten years



The number of studies that were gathered for each interval are added in parentheses

Table 6 demonstrates the placental weight from different studies between 1960 and 2017 and the gestational week of delivery. It is conspicuous that almost all gravidas delivered before term, in general around gestational week 37. Moreover, the maternal HbA1c value during pregnancy was higher in the first trimester than in the second or third trimester in all studies that were included in this work. Mehta et al. (2016) (32) observed a significant correlation between a first trimester HbA1c >8.5% and the placental weight at birth. In contrast they noticed a lower first trimester HbA1c in the group with a placental weight >736g compared to other groups with a lighter placental weight.

Figure 3 shows steady fluctuations of the placental weight in T1DM between the years 1960 and 2017 with a tendency towards heavier placentas between 1960 and 2010. The highest placental weight was found between the years 2001 and 2010 with an average placental weight of 637 grams. After 2010 the placental weight decreased again, with an average placental weight of 531 grams between 2011 and 2017. This decade included the highest number of examined placentas. A comparison between the development of the placental weight in a healthy control group and in T1DM was not taken into consideration in this work because of the lack of data. But it is worth mentioning that Swanson et al. (2008) (52) noticed an increase in placental weight from 499g to 537g (p=0.02) between the years 1995 and 2004 in healthy gravidae. They further found a significant increase of the maternal BMI during this period. Additionally, the mean gestational week at delivery did not change between the years 1975 and 2017. There were no data found before 1975.

Table 7 The calculated placental weight for the time period 1960-1990 and 1991-2017

Time Period	*Placental Weight in g*
1960-1990	596
1991-2017	560

g= gram

Table 7 shows the calculated mean placental weight for the years 1960-1990 and 1991-2017. Mean average values for each decade were multiplied with the number of investigated placentas for each decade. These values were summed and divided by the total number of investigated placentas for the two different time periods. The results show a decrease of 6% over time.

A representation of the development of maternal HbA1c from 1960 till 2017 was not possible. On the one hand due to a lack of data, on the other hand the values were measured

at different time points during gestation. Therefore, a presentation of reliable results was not feasible. It is noteworthy, though that all studies that mentioned HbA1c values for the different trimesters found higher values in the first trimester compared to the second and third.

7.4 Placental Structure in T1DM depending on the Maternal HbA1c

The altered environment caused by T1DM is known to have an impact on the placenta as well as on the fetus. Many studies have described the histopathologic abnormalities appearing in the placenta exposed to a diabetic milieu, but the underlying mechanisms are not fully understood yet.

Table 8 displays the papers that have been analyzed aiming at an assessment about the morphologic alterations in T1DM pregnancies. Although not all patients were defined as T1DM, all examined placentas were of mothers with IDDM or PGDM, which includes T1DM and T2DM, but as T2DM was not very common a few decades ago, most women with PGDM could be classified as T1DM.

The systemic review of placental pathology in maternal diabetes by Huynh et al. (2015) (53) already gave an overview about pathological changes in maternal diabetes. In the review the glycemic control was not classified by the maternal HbA1c, so this was taken into consideration in this work. The definitions of maternal HbA1c and its classification of excellent, good and non-optimal control were taken from Evers et al. (2003) (42). An excellent glycemic control was defined as a mean HbA1c value ≤6%, good control as values between 6.1 and 7% and a non-optimal control as HbA1c values >7%.

Table 8 illustrates that most women had a good glycemic control during pregnancy. Some studies defined the diabetes during pregnancy as well-controlled or good controlled but did not mention the HbA1c value. As a result, these studies are listed as ‘not specified’ in the table. Furthermore, the most published papers described an overall mean value for all examined women. Thus, it was not possible to state the exact HbA1c value of each woman. It is also noteworthy that not every published paper excluded women with other diseases such as chronic hypertension or preeclampsia or even integrated active smokers in their studies. These are mentioned in the column with additional information.

Table 8 Analyzed studies dealing with T1DM and the placental morphology in vivo grouped after the average maternal HbA1c during pregnancy

					Glycemic control und number of diabetic patients or the overall mean HbA1c value during gestation			
Authors, Year (Reference)	**Diabetes Classification**	**Total Number of Diabetic Placentas**	**Number of controls**	**Additional Information**	**Excellent ≤6%**	**Good 6,1-7%**	**Non-optimal >7%**	**Not specified**
Fox, 1969 (54) +	PGDM	48	234					48
Asmussen, 1982 (55) +	White D	9	unknown					9
Björk&Persson,1982 (56) +	White B White C White D White F	6 6 3 2	20					17 (MODD: 2.0-7.2mmol/l)
Björk&Persson, 1984 (57) +	White B White C White D White F	5 4 3 1	10	Median daily cigarette consumption was 3 (range 0-7)				13 (MODD: 2.4-7.2mmol/l)

Jirkovska, 1991 (58) +	T1DM	13	14					13 (well compensated)
Mayhew et al., 1994 (41) +	White A,B,C White D,F/R	39 16	34		Overall mean 5.6% (White A)	Overall mean 6.1% (White B), 6.4% (White C), 6.8% (White D, F/R)		
Younes et al., 1996 (59) +	PGDM	13	17	40% had a family history of diabetes 9 women had insulin treatment, 4 women were on diet			Overall mean 7.8 %	
Mayhew et al., 1998 (60) +	White B/C White D/F/R	4 6	6		Overall mean 6.0% (White B/C)	Overall mean 7.0% (White D/F/R)		
Mayhew et al., 2000 (61) +	White B+C White D+F+R	4 6	8		Overall mean 6.0% (White B, C)	Overall mean 7.0% (White D/F/R)		
Mayhew, 2002 (62) +	White B White C White D White F/R	10 7 11 6	34			Overall mean 6.1% (White B), 6.4% (White C), 6.8% (White D/F/R)		
Evers et al., 2003 (42) +	T1DM	58	38	33% of the women received insulin pump-therapy		Overall mean 6.3% (82% had excellent or good control)		

Maly et al., 2005 (43) +	PGDM	10	13					10 (well-controlled)
Jauniaux et al., 2006 (44) +	T1DM	12	10	7 pregnancies were complicated by polyhydramnions, 3 by chronic hypertension, 2 by preeclmapsia, 6 had macrosomic neonates			5 (>7%)	7 (good control)
Calderon et al., 2007 (63) +	PGDM (Overt Diabetes)	41	56	5 women were somekers, 16 suffered from srterial hypertension				41 (GGM= 122.1) [22 had an adequate glycemic control]
Nelson et al., 2009 (33) +	T1DM	88	39				Overall mean 7.1% (6.7-7.8)	
Dubova et al., 2011 (64) +	T1DM	12	6	All women used insulin pump-therapy				12
Higgins et al., 2011 (45) +	T1DM	10	10			3	7	
Rudge et al., 2011 (65) +	PGDM (Overt Diabetes)	83	6			Overall mean 6.2 % (calculated from an average of 122.1 mg/dl)		

Beauharnais et al., 2012 (47) +	T1DM	53	-	17% were hypertensive, 25% suffered from preeclampsia or eclampsia		Overall mean 6.8%		
Higgins et al., 2012 (48) +	PGDM	74	77	9 women had T2DM, 65 T1DM		Overall mean 6.5%		
Jirkovska et al., 2012 (46) +	T1DM	17	14		15	2		
Laurini et al., 1987 (38) —	White B-D	21	-	8 patients had pump-therapy before conception, 12 before 16th week of gestation, 1 in week 23 5 women were smokers 2 women developed PIH	1	8	11	1
Barth et al., 1996 (66) —	T1DM (White B-T)	47 (B=6, C=13, D=17, R,F,T=11)	-	Women with chronic hypertension or preeclampsia were not excluded				47
Gheorman et al., 2012 (67) —	T1DM	17	-					17 (HbA1c normal)
Starikov et al., 2014 (49) —	T1DM	117	-				Overall mean 8.3 % (7.2-9.6)	

Huyn et al., 2015 (50) —	T1DM	36	-	8 women suffered from preeclampsia, 2 women were active smokers		Overall mean 6.7%		
Jirkovska et al., 2016 (51) —	T1DM	16	8		14		2	
Basnet et al., 2015 (68) —	T1DM	39	-					39
Treesh&Khair, 2015 (69) —	Unclassified (controlled on insulin)	13	7					13
Starikov et al., 2017 (70) —	T1DM	117	-			15 (≤6.4%)	49 (6.5-8.4%) 53 (≥8.5%)	

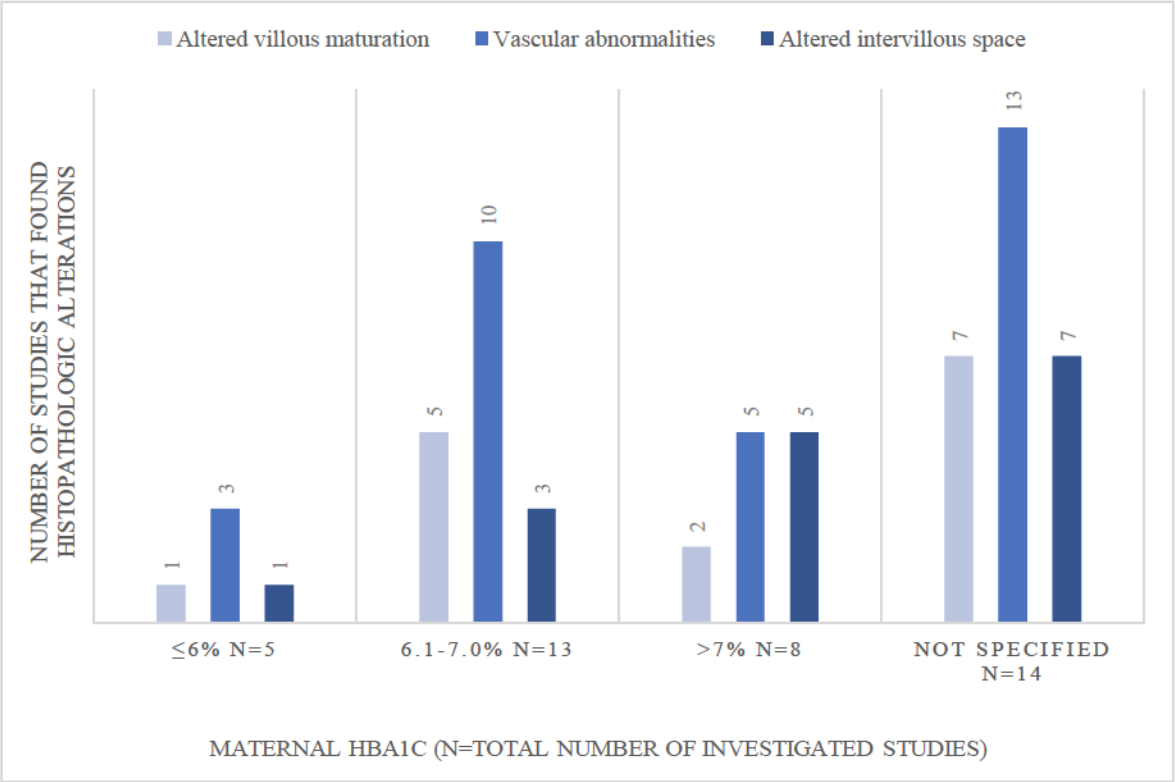
T1DM= type 1 diabetes mellitus, PGDM= pregestational diabetes mellitus, T2DM= type 2 diabetes mellitus, HbA1c= glycated hemoglobin A, MODD= mean of daily difference in blood glucose values, PIH= pregnancy induced hypertension

Studies that were already analyzed in the systemic review by Huynh et al. (53) are marked with "+". The added papers are marked with "-". Studies concerning T2DM, GDM or diabetes classified as White A were left out. Even studies which dealt with different types of diabetes were sorted and only the examined placentas of women with T1DM are mentioned.

After listing the studies dealing with placental morphology in women with T1DM and ranking them according to the maternal glycemic control, Figure 4 illustrates the significant morphologic findings according to Table 8. The diagram shows three main aspects of the placenta that are often influenced by pathologies in a pregnancy, such as diabetes. The horizontal axis shows the groups and total numbers of analyzed studies divided by the degree of glycemic control during pregnancy and the vertical axis demonstrates the number of studies that showed significant alterations according to these aspects. As it is shown in Table 8, some studies are listed in different groups because they indicated the exact HbA1c value of each woman or divided the women into different average values. For this reason, some of the studies are also enumerated more than once in Figure 4.

Altered villous maturation is defined by villous immaturity or villous hypermaturation. Vascular abnormalities comprise alterations in villous and capillary volume, surface area and length as well as the villous stroma and basement membrane. Furthermore, pathologies like syncytial knots, calcification and chorangiosis were ranked among the vascular abnormalities. The last group encompasses all abnormalities in the intervillous space, which includes altered intervillous volume and fibrinoid deposition. In all studies a p value ≤ 0.05 was defined as significant.

Figure 4 Pathologic morphologic findings from the studies mentioned in Table 8 regarding to the overall mean maternal HbA1c during pregnancy



The bar chart shows the number of studies that found significant alterations in T1DM placentas. N represents the total number of studies that were analyzed in the group. HbA1c= glycated hemoglobin A

7.4.1 Villous Maturation

During placental development in the first two trimesters in a normal pregnancy, mesenchymal villi transform into immature intermediate villi. They are defined by a loose stroma and increased capillary density, especially subtrophoblastic. From this state on they develop into stem villi. Hence, immature villi represent the starting point for growth and differentiation of various villous types. In the last trimester the mesenchymal villi start to produce mature intermediate villi, characterized by elongated unbranched capillaries, and the formation of terminal villi sharply increases. Therefore, immature villi are rarely seen histologically in healthy term placentas (71).

7.4.1.1 HbA1c ≤6%

A total number of five studies investigated placentas from women with an excellent glycemic control. Laurini et al. (1987) (38) discovered a relative villous immaturity in all placentas but only one woman of this study had a HbA1c value of 6.0%. Eight of the other women had

a good control and eleven a non-optimal glycemic control. The degree of villous immaturity did not relate to the White Classifications and therefore the duration of diabetes. The other studies did not find any significant difference between the diabetic and control group (60, 61) or did not investigate the villous maturation (46, 51).

7.4.1.2 HbA1c 6.1-7.0%

Women with T1DM who had a good glycemic control during pregnancy appeared as the biggest group in addition to the group with an unspecified HbA1c value. Five of thirteen studies in this group found significant changes regarding villous maturation. Beauharnais et al. (2012) (47) found placental dysmaturity in 29% in T1DM and 12% in T2DM (p=0.05). Huyn et al. (2015) (50) observed villous immaturity in 28% and villous hypermaturation in 11% of T1DM. Compared to 91% of villous immaturity and 2% of villous hypermaturation in GDM this reached a significant difference (p=<0.001, 0.02) but not towards T2DM (p=0.89, 0.14). It is noteworthy that in these two studies there was no healthy control group. Higgins et al. (2012) (48) noted the incidence of delayed villous maturation nearly doubled in PGDM towards the incidence of the control group. Furthermore, three other studies found a significant higher incidence of villous immaturity compared to a non-diabetic control group (38, 42, 45).

All other studies did not find any significant alteration regarding villous maturation in T1DM (41, 45, 46, 61, 62, 65, 70).

7.4.1.3 HbA1c >7%

A non-optimal glycemic control during pregnancy is defined as a HbA1c value >7%. In this work eight studies examined placentas of women in this group. Younes et al. (1996) (59) ascertained a mild villous immaturity in 19% of the cases and a moderate villous immaturity in 71% compared to 100% mature villi in non-diabetic mothers, but there was no differentiation between the preexisting diabetic and gestational diabetic mothers. The results of Laurini et al. (1987) (38) showed villous immaturity in all placentas. Higgins et al. (2011) (45) did not find any significant difference concerning the volume of immature intermediate villi, but the surface area of immature intermediate villi was significantly higher in the two diabetic groups compared to the non-diabetic group (p=0.007). There was no difference between T1DM and T2DM groups regarding villous immaturity.

Starikov et al. (2017) (70) analyzed placental pathology and perinatal outcomes in relation to maternal HbA1c in early pregnancies in women with T1DM or T2DM. A total number of 117 women with T1DM took part in the trial, 15 had a HbA1c value ≤6.4%, 49 6.5-8.5%, 53 had ≥8.5% in early pregnancy. The mean week of gestation during the HbA1c measurement was 9.5. Although most women did not have a good glycemic control, there was no significant difference in delayed villous maturation between the three groups (p=0.64). It is noteworthy that there was no control group. In accordance with these findings, the other studies did not find any significant alterations regarding villous maturity as well (33, 44, 49, 51).

7.4.1.4 Unspecified Maternal Glycemic Control

Some of the studies that were taken into consideration in this work, did not define the maternal glycemic control by the HbA1c value. A few of these papers defined the control as well controlled or normal HbA1c, but without precise information on the exact HbA1c values. Björk and Persson (1982,1984) (56, 57) expressed the degree of glycemic control as MODD (mean of daily difference in blood glucose values). These indicates the fluctuations of blood glucose levels from day to day. Besides the study from Björk and Persson (1982) six other studies found altered villous maturation (38, 43, 54, 66, 67).

The other studies in this group did not find any significant difference regarding villous maturation in T1DM, most likely because they focused their analysis on other aspects of placental morphology (44, 55, 57, 58, 63, 68, 69). These aspects are mentioned in the next paragraph dealing with vascular abnormalities.

7.4.2 Placental Vasculature

The placental villi, especially the terminal villi and fetal capillaries are the most important components of the placenta as they are assessed as the functional unit. In a term placenta terminal villi account for 40% of villous volume, 50% of total villous surface and 60% of villous cross sections. They have a high extent of capillarization and a small amount of stroma. Additionally, a discontinuous cytotrophoblast layer facilitates the feto-maternal exchange (72). Besides the terminal villi, the development of a capillary network is necessary to provide adjusted supply for the fetus. At the end of gestation the network has

emerged 550 kilometers in length and a 15m² surface area (73). Hence, altered placental vasculature can have a great impact on placental and fetal development and health.

7.4.2.1 HbA1c ≤6.0%

Jirkovska et al. (2012) (46) examined the villous capillary branching and structural alterations of terminal villi of 17 T1DM and 14 control term placentas. Two pathological forms of terminal villi were found in diabetic platencas, hypovascular and hypervascular villi. Both had a larger diameter than normal placental villi. The hypovascular villi were defined by a stroma that appeared like a meshwork with a high amount of loose stroma, their capillaries were thin and had a small diameter with narrow, wavy branches. Most of the thin capillaries were located close to the trophoblast layer, but some were situated distant with the inability to form vasculosyncytial membranes. The hypervascular villi presented with a small quantity of stroma. In this case the dominant structures were large and numerous, highly waved capillaries. In both pathological villi the collagen around the capillaries appeared thinner and the stromal network seemed to be less dense. Also, the redundant connections (RC) between capillary segments varied between diabetic and normal placentas. The mean number of RC per villous was significantly higher in the T1DM group.

Another study of Jirkovaska et al. (2016) (51) with 16 T1DM mothers and eight control analyzed the impact of T1DM on proliferative potential, differentiation and apoptotic activity in villous capillaries. They showed that in hypovascular as well as hypervascular villi, Ki67-labelled nuclei, a proliferation marker, were hardly seen in all compartments of the villous tree. Capillary differentiation was illustrated by the appearance of nestin, a cytoskeletal filament protein that emerges temporary in different cells during differentiation. The terminal villi of diabetic placentas showed a significantly higher proportion of nestin-positive segments of the capillary circumference compared to the control group. There was no significant distinction between T1DM and control regarding the number of apoptotic trophoblasts, stromal or vascular cells.

Laurini et al. (1987) (38) described several vascular abnormalities in the diabetic placentas. All placentas showed focal thickening of the trophoblast basement membrane, nine placentas had variable degrees of ‘endarteritis’ of chorionic villi. There was a high prevalence of centrally located non-dilated fetal capillaries with badly devised vasculosyncytial membranes. This result matches to the relative villous immaturity found in all placentas. Additionally, hypovascular villi were seen in this study as well.

Mayhew et al. (1998, 2000) (60, 61) did not ascertain significant differences regarding vascular features between the diabetes and control group.

7.4.2.2 HbA1c 6.1-7.0%

The most common findings in the group of women with a good glycemic control were a significant increase of capillary volume, capillary surface area, a greater surface area of terminal villi and immature intermediate villi. In addition, nucleated red blood cells and chorangiosis were significantly more frequent in T1DM compared to a healthy control group (41, 42, 45, 50, 62). Rudge et al. (2011) (65) investigated 22 histopathological aspects among four different groups, women with normoglycemia, mild gestational hyperglycemia, gestational diabetes mellitus and overt diabetes (PGDM). All 22 histopathologic aspects were observed in the overt diabetes group and some of them were just seen in this group (chorial edema, intima edema, hofbauer cell hyperplasia, villitis), but the only results that varied significantly between the four groups were subchorial infarct, calcification, syncytial nodes, endarteritis and duplicate membrane. Especially calcification was very common in overt diabetes but was also seen in the normoglycemic group. Besides, there were no significant differences regarding the Index of Placental Changes (IPC) between the four groups considering gestational age and glycemic control. The IPC was used to describe placental lesions for each category. The 'Total Score' means the total number of histopathological findings for a group of patients and 37 reflects the number of lesions that could potentially be distinguished.

$$IPC = \frac{Total\ Score\ \times\ 100}{(37 \times n)}$$

Furthermore, some studies investigated the differences between T1DM and T2DM. The most pathological findings did not differ between the two groups (45, 50). Beauharnais et al. (2012) (47) observed more placental infarcts in T2DM than T1DM. The other studies that found vascular abnormalities in good controlled T1DM women were already mentioned in the excellent controlled group (38, 46). Some studies did not observe any significant vascular abnormality in T1DM compared to a non-diabetic control group (60, 61, 70).

7.4.2.3 HbA1c >7%

Nelson et al. (2009) (33) investigated the placental stereology of mothers with T1DM and healthy control mothers. Capillary volume and surface were similar between the two groups, but capillary surface area relative to capillary volume was reduced in T1DM (p=0.01). Furthermore, the villous coefficient (cm^3/cm^3) and villous elaboration index were significantly reduced in T1DM (p=0.025, p=0.019). These values were used to demonstrate the branching of the villous trees.

Jauniaux and Burton (2006) (44) examined the placentas from twelve women with T1DM and ten control placentas. Five women with T1DM had macrosomic infants. Placental volume and trophoblast volume were significantly increased in the diabetic group in general (p<0.05). Moreover, the placentas of the five women with macrosomic infants showed a significant increased volume of intermediate and terminal villi (p<0.01), an increased villi and capillary surface area (p<0.05), as well as an elevated morphometric diffusing capacity (p<0.05).

Younes et al. (1996) (59) discovered a basement membrane (BM) thickening in diabetic placentas compared to the control group (p<0.05). Both membranes of terminal villi, the trophoblast basement membrane (TBM) and capillary basement membrane (CBM) were affected. This was more prominent in GDM than in PGDM. The remaining studies in this group were already mentioned in the group with excellent or good glycemic control (38, 45, 51).

Starikov et al. (2017) (70) examined 117 placentas from T1DM mother with different degrees of glycemic control. Most women had a HbA1c value between 6.5-8.4% (39.8%) or ≥8.5% (52.0%). Various histopathologic alterations were seen in many T1DM placentas, for example decidual vasculopathy, increased perivillous fibrin deposition, basal plate with fibrin deposition and increased extravillous trophoblast or increased syncytial knots. But except from acute chorioamnionitis (p=0.03), none of the placental findings reached statistical significance between the three groups.

Table 9 Placenta change index HbA1c Level, extracted from Starikov et al. (2017) (70)

Variable	6.4 (n= 68)	6.5-8.4 (n= 123)	≥8.5 (n= 102)	P-Value
Index of Placental Changes	10.5%	10.1%	10.4%	0.70

HbA1c=glycated hemoglobin A

Table 9 shows that there were no significant differences regarding the IPC between the three groups. T1DM and T2DM were combined in this table (70).

Another study from Starikov et al. (2014) (49) compared the placentas of gravidas with T1DM and T2DM. Although the overall HbA1c value of 8.3% (7.2-9.6%) in T1DM was significantly increased compared to 7.1% (6.3-8.6) in T2DM (p<0.0001), none of the histopathological findings was observed significantly more frequent in T1DM. T2DM placentas showed a decidual vasculopathy more commonly than T1DM (p=0.002). However, it must be emphasized that these studies die not have a control group.

7.4.2.4 Unspecified Maternal Glycemic Control

In most instances the women in the group with an unclassified HbA1c were indicated as well or good controlled by the authors. Nevertheless, vascular abnormalities were observed very often in this group. The most common findings were an increased number of villous capillaries, especially those of a small perimeter, but a decreased mean and total area of villi, indicating a predominance of branching angiogenesis. Additionally, villous edema, intravillous fibrinoid, thickening of throphoblast basement membrane or a thinner capillary basement membrane were observed often (38, 44, 54, 55, 58, 63, 64, 67, 69).

Björk and Persson (1984) (57) investigated the villous structure in different parts of the cotelydon. In normal placentas the length of the villi increased towards the periphery of the cotelydon, unlike the insulin-dependent diabetes group. Their villous length stayed quite the same in the central (C), intermediate (M) and lateral (L) region. In contrast the surface area grew from C to L in normal placentas, whereby the diabetic placentas showed opposite phenomenon with the greatest surface area in the C region. The diabetic placentas had a 25% grater mean area for all three regions in total. This result showed a linear correlation with the MODD (mean of daily difference), a value for daily glucose fluctuations, from the 12th to 32nd gestational week. Another study of Björk and Persson (1982) (56) showed a significant increase of vasculosyncytial membranes and syncytial knots with higher values of MODD from 12th to 32nd week of gestation, but there was no correlation between placental alterations and the MODD from the 32nd week until term. Calderon et al. (2007) (63) measured an significant elevated GGM (gestational glycemic mean) in OD compared to control, MH and GDM with an average value of 122.1 mg/dL (p=0.05) whereby a GGM <120 mg/dL was defined as inadequate. On the one hand the MH group had a significant greater total area (p=0.0067) and number of terminal villi (p=0.0001) as well as a smaller

mean area of terminal villi (p=0.0001), on the other hand total area and mean area of villi vessels were smaller in both diabetic groups (p=0.0001). The ratio of total area of villous vessels and terminal villi, defined as the capillarization index (%), was decremented in OD compared to the other groups. In this study, only the total area of terminal villi correlated directly with maternal GGM in OD (p=0.044).

Further vascular abnormalities that were seen in T1DM were pathological abnormalities of the decidual arteries. Barth et al. (1996) (66) found mildly abnormal arteries (type A) in 23% of the cases, which was defined by thickening or hyalinization of the arterial wall. In 11% severely abnormal arteries (type B) occurred, with thrombosis, fibrinoid necrosis or atherosis with foamy histiocytes. Therefore, 66% had normal decidual arteries.

7.4.3 Intervillous Space

7.4.3.1 HbA1c ≤6.0%

In this group there was one study that investigated the intervillous space in detail, especially the spatial relationship between the villi and intervillous space. The global volume, as well as the fibrinoid volume (cm^3) seemed to be greater in the diabetic group compared to control, but these results did not reach statistical significance. The fibrin-type fibrinoid content, though, varied between the two groups (61). Laurini et al. (1987) (38) found an increased distance between the intervillous space and fetal capillaries.

The remaining studies in this group did not show any significant alterations or did not investigate the intervillous space (46, 51, 60).

7.4.3.2 HbA1c 6.1-7.0%

In the group with good controlled T1DM only three of the thirteen studies found a significant alteration regarding the intervillous space (38, 42, 45). For example Higgins et al. (2011) (45) measured an increased absolute intervillous volume (p=0.00) in the diabetic compared to control group.

Rudge et al. (2011) (65) found intervillous fibrosis in 78.3% of the cases in the overt diabetes group. Although this was a very common finding, it did not reach statistical significance because 50% of the normoglycemic placentas showed intervillous fibrosis as

well. The remaining studies including the good controlled women showed comparable findings. They did not show significant alterations or did not analyze the intervillous space (41, 46–50, 60, 62, 70).

7.4.3.3 HbA1c >7%

The group of studies that included the women with a non-optimal glycemic control contained five studies that mentioned a significant altered intervillous space. Some of them were already mentioned in the other groups (38, 45). Nelson et al. (2009) and Jauniaux and Burton (2005) (33, 44) both found a significant increase in the intervillous space volume (p=0.02, p<0.05) in T1DM compared to a non-diabetic control group. Especially the placentas from macrosomic infants showed an extreme elevated intervillous space volume (p<0.005) (44). Younes et al. (1996) (59) examined fibrinoid material in the intervillous space in 90% of the diabetic placentas, but it was more common in GDM than in PGDM.

The remaining studies did not show any significant change (49, 51, 70).

7.4.3.4 Unspecified Maternal Glycemic Control

In the group with an unknown HbA1c, common findings regarding the intervillous space were a reduced intervillous space volume and fibrinoid (57, 64, 67). Furthermore, intervillous thrombi were detected more often in T1DM than in control (44, 54, 66). Basnet et al. (2016) (68) observed a significant higher incidence of intervillous thrombi in diabetes in general compared to control (p=0.03). The incidence was also increased in T1DM (4/39, 10.3%) compared to controls (7/99, 7.1%), but this did not reach significance.

7.4.4. Comparison Between Excellent, Good or Non-Optimal Controlled T1DM

Analysis of the different studies dealing with placental morphologic alterations in women with T1DM showed that abnormalities appeared in all three groups. The trials with undefined glycemic control are left out in this part to focus on the role of maternal HbA1c value. The group with good control, defined by a HbA1c range from 6.1% to 7%, comprised the highest number of studies and additionally the highest number of pathologic changes, taken together all three groups of alterations. These include maturation disorders, vascular abnormalities and alterations of the intervillous space. Further, this group contained the most

studies showing altered villous maturation. Vascular abnormalities were the most common findings in the excellent and well controlled group. In the non-optimal controlled group, they were equally with intervillous alterations. The altered intervillous space was mostly found by studies belonging to the non-optimal controlled group. A significant, unambiguous correlation between placental morphology and the average maternal HbA1c value in T1DM could not be established.

7.4.5 The Impact of First, Second and Third Trimester HbA1c

7.4.5.1 Perinatal Outcome

The previous paragraph described pathologic alterations of placentas regarding the average HbA1c value during pregnancy in women with T1DM. This paragraph analyses the question if there is a sensitive time period for the HbA1c leading to placental pathologies.

The first trimester or even pre-conceptional HbA1c seems to be more important than second or third with a view to the perinatal outcome. The newborn's birthweight, the risk for macrosomia as well as the incidence of fetal malformations did significantly correlate with the first trimester HbA1c in different studies (74–76). Likewise, the risk for spontaneous abortion and adverse pregnancy outcome was significantly higher in T1DM who had a poor glycemic control in the early pregnancy. A reduction of the HbA1c by 1% in the early pregnancy decreased the odds ratio for preeclampsia to 0.6 (77–80). One study found a more precise time point at the end of the first trimester. Mothers with babies above the 90th percentile for weight had a higher HbA1c at that point than mothers with neonates below the 90th percentile (81). Additionally, the pre-conceptional glycemic control effects the newborns birthweight and values >6.9% did significantly raise the risk for adverse pregnancy outcome. It further increased the risk for fetal and infant death (15, 39, 82).

Another study ascertained the average HbA1c was a little higher than in control, but was mostly excellent or good controlled and still the rate of macrosomic neonates was 48.8% (according to growth charts from 1998) (83). In addition, first and second trimester mean glucose as well as the maternal weight at delivery did correlate with the birthweight (75). One study found a significant correlation between maternal weight gain during pregnancy, weight at delivery and a non-optimal glycemic control in the first and third trimester (31).

Controversially, further studies observed a significant correlation between the third trimester HbA1c and the risk for macrosomia, LGA infants, deliveries <37 weeks or neonatal

complications. Especially HbA1c values rising from 4.5% to 7% seem to have a linear correlation (84–86).

According to an average HbA1c, an association with adverse pregnancy outcome and birth weight was observed as well (87–89). An increase of 1% HbA1c profoundly increases the risk for adverse pregnancy outcome by 5.5% (87).

7.4.5.2 Placental Morphology

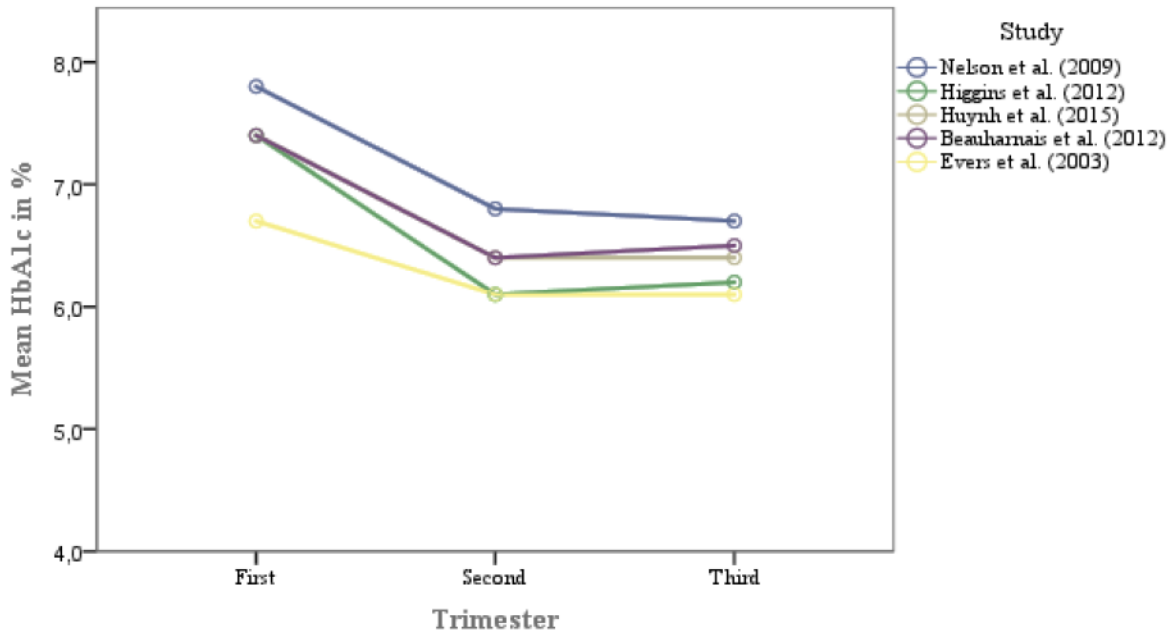
Table 10 The average HbA1c value in first, second and third trimester in women with T1DM

Trimester	*Average HbA1c in %*
First	7.3
Second	6.3
Third	6.4

HbA1c= glycated hemoglobin A, References (33, 42, 47, 48, 50)

Table 10 shows the different HbA1c values measured from women with T1DM at different time points during pregnancy. All data were collected from the five studies that mentioned a maternal HbA1c value in all three trimesters. The medium of these results was calculated and summarized in Table 10. It evinces that the HbA1c value was higher in the first trimester compared to second and third trimester, but the values between the second and third trimester did not differ notably.

Figure 5 The development of maternal HbA1c values from first to third trimester in T1DM pregnancies, compiled from different study results



HbA1c= glycated hemoglobin A

For a better representation of the development of maternal HbA1c, all data are further presented graphically. This is shown in Figure 5. This graphic demonstrates the fall of the HbA1c value from the first to the second trimester. The vertical axis shows the mean HbA1c value measured in the three trimesters which starts with a value of four percent to improve the presentation.

The results raise the question whether a higher first trimester effects the placental morphology. All studies found an altered placental morphology in T1DM, for example a significant higher placental weight, nucleated red blood cells, fibrinoid necrosis, villous immaturity or chorangiosis (33, 42, 47, 48, 50). Only two studies mentioned an association between the maternal HbA1c at a specific time period and placental changes. Evers et al. (2003) (42) observed in the diabetes group itself that the mean HbA1c and third trimester HbA1c were significantly higher in the group with LGA infants compared to the group with AGA infants. Nelson et al. (2009) (33) mentioned an association between the maternal HbA1c at 26 to 34 weeks and the birthweight, placental weight and intervillous space volume. The other studies showed a significant increased first trimester HbA1c value and found placental changes in T1DM. But they did not describe a correlation between the maternal HbA1c and placental alterations. This was mostly because the focus of their works was not the role of maternal HbA1c.

The study from Starikov et al. (2017) (70) showed that there were no significant variations in placental lesions regarding higher HbA1c values, although most women with T1DM had a HbA1c ≥8.4%. They classified the women after their HbA1c value and calculated the average gestational week the HbA1c was determined. The average gestational age was 10.1 weeks for HbA1c levels ≤6.4%, 8.4 weeks for 6.5-8.4% and 7.8 weeks for ≥8.5% (p=0.008). They only mentioned first trimester HbA1c values. Therefore, this study is not mentioned in Table 10. It is noteworthy that women with a high HbA1c had higher fasting and 2-h postpandrial blood glucose values later in pregnancy.

It is appreciable though that Björk and Persson (1982, 1984) (56, 57) found a significant correlation between an elevated MODD (mean of daily difference in blood glucose values) among the gestational weeks 12-32 and a higher number of villi with vasculosyncytial membranes, syncytial knots and a linear correlation to the combined central (C), intermediate (I) and lateral (L) region of the cotyledon. The villous length was rather similar in all three regions, whereas the villous length in normal placentas increased with a greater distance from the center. The villous surface area seemed to decrease towards the lateral region in diabetic placentas. The control placentas showed the exact opposite result with a trend towards the periphery. These pathologies did not correlate with an elevated MODD from 32nd week till the end of gestation.

In addition to histological examinations after birth, other methods were needed to analyze the effect of first trimester HbA1c on the placenta. 3D-power Doppler sonography represents a useful method to quantify placental volume and vascular abnormalities. In one study using the technology, the placental volume did not differ between T1DM compared to reference limits, but 3D Doppler showed a significant increase in vascular indices in T1DM, measured in the first trimester. Especially diabetic mothers with HbA1c ≥7% compared to diabetic mothers with HbA1c <7% in first trimester had increased vascular indices. This reflects an increased vascularization in T1DM (90).

These results show that the glycemic control of women with T1DM is of an important relevance for the newborn's outcome. Regarding the placental alterations, the role of a first trimester HbA1c is difficult to represent. All studies showed a significant increased first trimester HbA1c. But the association between placental alterations and the HbA1c value at different time periods during gestation could not always be traced back to the first trimester HbA1c. The role of pre-conceptional HbA1c and placental abnormalities cannot be answered in this work because currently there are no studies published dealing with this topic.

7.5 The Effects of Fetal Sex

The previous chapters are dealing with the influence of maternal characteristics, especially the glycemic control, on placental structure. Hereinafter, this chapter is following up on the issue if and how fetal characteristics influence the placenta. This work focuses on the effect of the fetal sex.

7.5.1 Perinatal Outcome

Considering the perinatal outcome in neonates born by mothers with T1DM, Persson et al. (2014) (91) observed a significant higher incidence for caesarean section, respiratory distress or transient tachypnoea in male neonates compared to female. The composite morbidity, which includes perinatal death, major malformation, preterm delivery (<37 weeks), acute respiratory disorders or neonatal hypoglycemia, was 36.5% in male infants compared to 33.1% in female infants (p=0.022). In addition to 4092 T1DM mothers, 412 T2DM, 8602 GDM and 905 565 mothers without diabetes were included in the study. For the sake of completeness, it is noteworthy that male infants from T1DM and GDM mothers had significantly increased incidence for respiratory distress. The number of major malformations was also elevated in male neonates in GDM. The rates of adverse outcome were higher in male infants from T2DM mothers compared to female as well, but they did not reach significance. In the control group without diabetes all adverse outcomes, except for the perinatal mortality rate, were significantly higher in male neonates compared to female neonates.

Additionally, further studies investigated the perinatal outcome infants in T1DM. Nearly all of the analyzed characteristics concerning an adverse outcome were more common in male infants, but only the composite outcome in the total cohort of PGDM (T1DM+T2DM) reached statistical significance (<0.05) (22). Another study found a significant higher incidence of congenital malformations, preterm delivery and respiratory disorders in male neonates compared females in pregnancies complicated by T1DM. The incidence of congenital malformations was 12.7% in male infants and 3.0% in female infants. The incidence in females almost correlated with the incidence in the national population (2.6%) (92). The number of stillbirths was also higher in males, 59% of the stillbirths were associated with the male sex. Therefore, the male sex constituted an

independent risk factor for stillbirth. Most stillbirths in male fetuses took place at a later gestational week than in females, median was 30.2 weeks in male compared to 25 weeks in female stillbirths (p=0.01), 20% of the stillbirths in male fetuses appeared between the weeks 37-40. In these cases, 11% were associated with PGDM and 32% with IUGR. Hence, T1DM was an independent risk factor for stillbirth as well (p=0.006) (93). In T1DM the birthweight of male newborns was also significantly higher than in female newborns (3367.5g vs. 3260g) (p=0.005), as well as the incidence of macrosomia (15.5% vs. 7.3) (p=0.01) (94).

In all studies that were taken into consideration for this work, the maternal characteristics, such as maternal BMI, weight gain, HbA1c values or duration of diabetes, did not differ significantly between male and female infants.

7.5.2 Placental Morphology

The studies have shown, that the outcome in male infants is worse compared to female infants. This was seen in healthy women and even in women with T1DM. This raises the question, if the fetal sex effects the placental morphology just as.

Studies ascertained a severe placental dysfunction more often in male than in female (95, 96). The severe placental dysfunction was defined by an absent or reversed end-diastolic flow (AREDF) in the umbilical artery, which was determined by Doppler ultrasound. A significant higher birthweight/placental weight (BW/PW) ratio was observed in male infants compared to females. Male and female infants with severe placental dysfunction had a significant higher BW/PW ratio compared to the control group as well. But males were significantly more affected than females (96). Additionally, in pregnancies affected by preeclampsia or IUGR, chronic deciduitis and velamentous insertion of the umbilical cord appeared more frequent in male, although placental development and differentiation did not vary between the two groups. In contrast, villous infarction was rarer in male than in female (97).

Some recent papers found a positive association between the transcription of the growth receptor binding protein 10 (GRB10), which plays an important role for fetal growth, and placental weight, birth weight and neonatal head circumference. Regarding the fetus sex, the association between placental weight, birth weight and placental GRB10 transcription was only significant in male fetuses. Male SGA placentas had lower GRB10 levels than male AGA placentas (98). Furthermore, the review of Kalisch-Smith et al. (2017) (99) showed that placentas from male and female fetuses form, function and adapt differently in general.

Male fetuses had higher placental weight and a higher metabolic rate. Thus, they seem to be more vulnerable to oxidative stress when nutrients are limited. It is suggested that females are more susceptible to disturbances in the peri-conceptional period, whereas disturbances at a later point of gestation seem to have a greater effect on the placenta from male fetuses.

Regarding the placental morphology in T1DM only one study could be found for this work that distinguished between males and females. Mayhew et al. (1993) (40) investigated the effects of the mode of delivery and the fetal sex in diabetic and control pregnancies. A total number of eleven diabetic cases and 34 control cases were included. Taken together, all women delivered 24 males and 21 females. The diabetes group was classified as White D with a mean HbA1c of 7% over gestation. Maternal and neonatal characteristics did not differ significantly in association with the mode of delivery or fetal sex. The diabetic placentas in general had a higher weight, shorter fetal plasma distances and larger fetal capillaries compared to the control group. Significant differences between male and female were higher values in the maternal plasma distance, fetal capillary volume, fetal capillary surface area, the distance across the stroma and the diameter of fetal capillaries in the male. Placentas from male infants were heavier than from females (535g vs. 496g), but this result did not reach statistical significance.

7.6 Placental Angiogenesis in T1DM

7.6.1 Physiology of Placental Angiogenesis

The formation of new vessels, called vasculogenesis, and its further development and sprouting, the angiogenesis, culminating in the placental structure at the end of gestation, are complex mechanisms. Therefore, the physiologic basis is just mentioned briefly in this work.

The vasculogenesis starts around the 21st day post conception. It is characterized by the differentiation of haemangiogenic stem cells, which descend from pluripotent mesenchymal progenitor cells, into early primitive capillaries (100, 101). The haemangionic stem cells further differentiate into haemangioblastic stem cells and further into angioblastic cells, the precursor cells of endothelial cells. The haemangioblastic stem cells furthermore differentiate into haemangioblastic cells, the precursor cells of haematopoietic cells (101). An elongation is accomplished by the combination of replication and recruitment of stromal

cells (73). After the formation of the primary vessels, new vessels develop originating in these first vessel. The process, called angiogenesis, continues until delivery.

Different growth factors regulate and stimulate the process of angiogenesis (100). The main growth factor influencing vasculogenesis and angiogenesis is the vascular endothelial growth factor (VEGF). It consists of different subgroups, but most important for placental vascular development are VEGF-A, PIGF, and the receptors VEGFR-I and VEGFR-2, also called Flt-1 and kinase insert domain receptor KDR. VEGF-A (often just called VEGF) initiates the differentiation of mesenchymal progenitor cells into haemangioblastic stem cells. During the first trimester it is expressed by villous trophoblasts, at a later stage it seems to be expressed by macrophages and other mesenchymal cells (100). It works as a mitogen for endothelial cells, therefore promotes angiogenetic remodeling and the development of a capillary network, especially the branching angiogenesis, which is predominant till the 25th week of gestation. Afterwards PIGF seems to play a more important role in angiogenesis because the expression of PIGF binding to Flt-1 increases towards the end of gestation with its peak at the beginning of the third trimester. It consists of three different isoforms, PIGF1, PIGF2 and the newly described PIGF3. It is secreted by syncytiotrophoblasts and is responsible for the development of a highly branched capillary network (73, 100–104).

Besides the VEGF system, other growth factors play a role in the development of the placental vasculature as well. The fibroblast growth factor (FGF) is one example worth mentioning. It consists of different isoforms. FGF-1 and FGF-2 for instance were found in the cytotrophoblast and extravillous cytotrophoblast, occurring after the invasion of the cytotrophoblast into the decidua in the first trimester. At the end of gestation, they were found in syncytiotrophoblast, hofbauer cells and vessel's media. They seem to stimulate cell proliferation, reduce extracellular matrix, be involved in migration and modulation of cell-cell interaction and cytotrophoblast invasion (100, 104).

Furthermore, fetal insulin and IGFs have an influence on placental and fetal growth and development. While IGF1 and IGF2 are secreted by mesenchymal cells, their receptor, IGF1R, one isoform that works as a signaling receptor for IGF1 and IGF2, is expressed on villous cytotrophoblast, syncytiotrophoblast and extravillous cytotrophoblast and in the third trimester additively on placental macrophages and fetoplacental endothelium. The receptor for insulin, IR, is expressed mainly on the syncytiotrophoblast at first and at the end of gestation primary in fetoplacental vessels. The insulin/IGF system has a metabolic, mitogenic and anabolic effect (100, 105, 106). IGF-1 and IGF-2 increase the proliferation of the cytotrophoblast and inhibit its apoptosis (107).

Placental growth hormone (PGH) is secreted by the syncytiotrophoblast continuously, it replaces the pituitary growth hormone (hGH) from mid-gestation onward with a steady increase towards term. It does not have a direct effect on the fetal growth, but it has a somatotropic effect on the maternal metabolism, by increasing gluconeogenesis and lipolysis and further a paracrine effect by stimulating the formation of IGF-1 and IGF-2 (108–111).

7.6.2 VEGF, PIGF and FGF in T1DM

It was already mentioned that the placental vasculature is changed in women with T1DM. Mayhew (2002) (62) found a significant increased capillary volume, surface area and length, but mean area, perimeter and shape factor in cross section, reflecting vascular remodeling, did not differ between the T1DM group and the control group. Further, the capillary to villous length ratio in the diabetic group showed that the growth of capillary length surpasses the growth of villous, indicating a longitudinal growth of vasculature and no augmented vascular remodeling.

The placental growth factor VEGF was increased in women with T1DM, especially in infants with a birthweight >4000g (112, 113). Additionally, VEGF was highly positive in structures of the terminal villi, mostly in the syncytiotrophoblast. The VEGFR-2, the main transmitter for the mitogenic and angiogenic effects of VEGF, showed the highest intensity of all analyzed VEGFRs (VEGFR-1, VEGFR-2, VEGFR-3). The most intensive expression of VEGFR-2 was found in mesenchymal cells of terminal villi. Both, VEGF and VEGFR were mostly expressed in cells of terminal villi and surpassed the levels of physiologic pregnancy, but the increase of this expression was different between the different cell types of the terminal villi (114, 115). Additionally, Leach (2011) (115) found elevated VEGF levels in fetal vessels.

Maternal hyperglycemia, the major problem in all diabetes types, leads to fetal hyperglycemia and further to fetal hyperinsulinemia. The fetal insulin secretion begins at the end of the first trimester. Fetal hyperglycemia and fetal hyperinsulinemia result in an enhanced metabolic rate and thus in a higher oxygen demand. This condition often forms a basis for chronic fetal hypoxia (100). Hypoxia represents the strongest stimulator for angiogenesis, which can result in an increase of VEGF in hypoxic environments (62, 100, 104). Hypoxia induces the expression of HIF-1, which activates genes that are involved in placental angiogenesis, for example VEGF or sFlt-1 (116–118). The existence of fetal hypoxia in T1DM has been shown by elevated erythropoietin levels in amniotic fluid or cord

serum, elevated cord leptin levels or the presence of nucleated red blood cells in the placenta (42, 119–121).

Furthermore, visfatin, also known as pre-B cell colony enhancing factor (PBEF) or nicotinamide phosphoribosyltransferase (NAMPT), functions as an adipokine and as a cytokine. The adipokine is secreted by the visceral fat with a similar effect to insulin (122). In the placenta, it is mainly expressed by the amnion and works as a stress-responsive cytokine, thus induced by hypoxia (123, 124). One study found out that in a hypoxic environment PBEF may stimulate the secretion of VEGF by the amnion, resulting in a higher permeability of the amnion that could further lead to amnion fluid volume disorders (125). Additionally, another study found the highest expression of PBEF in women with T1DM who had SGA and LGA infants ($p<0.05$), but neonates with a birthweight >4000g had the lowest visfatin expression (<0.055) (126). The reduction of soluble Flt-1 (sFlt-1) and soluble VEGFR-1 (sVEGFR-1) by suppressing its expression was found to be induced by hypoxia as well. They bind VEGF extracellularly and therefore work as anti-angiogenic factors (127, 127, 128).

The growth factor PIGF, belonging to the VEGF family, was altered in pregnancies with PGDM compared to control, likewise. But it was striking, that elevated PIGF levels occurred only towards the end of gestation. James-Todd et al. (2016) (129) found elevated serum PIGF levels from the gestational week 27 onward in PGDM compared to a healthy control group. These elevations also correlated significantly with the birth weight percentiles, weeks 27-34 ($p=0.02$) and 34-40 ($p=0.009$) and additionally, high PIGF values at the late third trimester were significantly associated with a higher risk for macrosomic neonates in the diabetes group. Further studies found higher sFlt1/PIGF ratios in the preexisting diabetes group without preeclampsia compared to a healthy control group and even higher values in T1DM with preeclampsia compared to T1DM without preeclampsia (130, 131). These results correspond to the decreased PIGF levels in the second trimester in SGA neonates compared to non-SGA neonates in T1DM, but similar values in the first trimester (132). Kuc et al. (2011) (133) wanted to predict macrosomia at birth with the measurement of biomarkers of early placentation in PGDM. Even though the rate for macrosomia was 42.6% in PGDM compared to 18.3% in the control group ($p<0.0001$), the PIGF values did not differ between the groups in the early state of pregnancy. These results all point to a possible role of PIGF at a later stage of pregnancy, leading to an increased birth weight. Despite the PIGF levels in maternal serum, PIGF concentration of cord serum at birth did not differ between T1DM and healthy pregnancies (134).

Elevated levels of FGF2 were observed in maternal serum, in cord serum and in amniotic fluid in T1DM pregnancies (100, 135, 136). Placentas from T1DM women showed a higher expression for FGF2 and FGFR1 as well, especially the syncytiotrophoblast and villous stroma displayed an increased intensity (137, 138).

7.6.4 Insulin and the PGH/IGF Axis in T1DM

The fetal hyperinsulinemia does not occur due to changes of placental transporters, but to the elevated transfer of glucose leading to fetal hyperglycemia and stimulating the formation of fetal insulin (139). The fetal hyperinsulinemia leads to a fetal glucose steal, which means a permanent glucose uptake even during normal maternal glucose levels (140). Fetal hyperinsulinemia has further been shown by high cord insulin levels, which correlated with the perinatal outcome, especially neonates with a severe hyperinsulinemia (>50µU/mL) had considerable higher rates of complications (141).

Not only the resulting higher oxygen demand caused by the fetal hyperinsulinemia influenced placental angiogenesis, but the fetal insulin seemed to play a role itself. Insulin stimulated angiogenesis through the activation of different signaling pathways. One example was the activation of endothelial nitric oxide synthase (eNOS), which activated the hypoxia inducible factor 1 (HIF-1). This, in turn, stimulated the secretion of VEGF (105, 142). Further, insulin regulated the ephrin-B2 expression, which is a molecule especially involved in arterial sprouting, as well as the expression of insulin receptor and VEGF, indicating an angiogenesis originating from arteries (139). Microscopically, insulin led to a significant increased capillary surface area (33) and in vitro to an increased tube length of the network formation and increased branching (142). Hiden et al. (2009) (105) observed a denser expression of the insulin receptor (IR) in the syncytiotrophoblast in the first trimester changing towards a higher expression in the endothelial cells in the third trimester. This indicates a switch in regulation of insulin effects.

In T1DM placentas in the first trimester showed a significantly increased expression of matrix metalloproteinase (MT1-MMP), upregulated by insulin and tumor necrosis factor alpha (TNFα) (105, 143). Pro-MT1-MMP can be activated by furin. Its transcription, in turn, is modified by HIF-1 (116). Matrix metalloproteinases degrade structural components of the extracellular matrix through proteolysis. Thus, they can regulate tissue architecture. They can in addition activate, deactivate or modify the activity of signaling molecules and can effect cellular functions by regulating proteins of the extracellular matrix (144). MT1-MMP,

a subfamily of MMP, plays an important role during angiogenesis by enhancing endothelial migration (145) and the activation of MMPs, which have a proteolytic effect (146). A recently published paper observed an activation of MT1-MMP itself by the metabolite prostaglandin E2 (PGE2) inducing neovascularization (147).

In T1DM the IGF-1 levels in the maternal serum were lower than in control women and it further decreased from the first to the second trimester and increased again in the third trimester (106, 148, 149). IGF-1 levels in the fetal cord serum were increased in women with T1DM (106, 150). The increase of IGF-1 in the maternal serum in the third trimester significantly correlated with the increase of PGH in the third trimester (108, 109, 148). PGH seems to play an important role in the development of insulin resistance in diabetic pregnancies (108). Additionally, different studies showed a positive correlation between maternal serum concentration of IGF-1 and PGH and the neonates birth weight in T1DM (33, 106, 108, 148, 151–155). Ringholm et al. (2015) (156) observed an association between lower PGH levels at an early stage of pregnancy and higher rates of LGA infants in T1DM. Furthermore, IGF-1 and PGH seem to influence the placental weight positively (33, 148, 151). Nelson et al. (33) did a histological examination of the placenta and analyzed the effect of IGF-1 on the microscopical structure. It revealed that higher IGF-1concentrations were associated with altered villous volume, intervillous space volume, nonparenchymal volume and capillary volume.

7.6.5 Angiogenesis Depending on Maternal HbA1c in T1DM

Results discussed in the previous section showed that different angiogenic factors are altered in pregnancies complicated by T1DM. This raises the question whether these alterations are correlated to the maternal HbA1c value during pregnancy.

Concerning the angiogenic factor VEGF, some studies found a significant correlation between the mean HbA1c or fasting blood glucose values (113, 157). Others found a correlation between the third trimester placental VEGF concentration and the mean blood glucose and HbA1c values, but not first or second trimester (112, 114). In contrast to the correlation between VEGF and maternal HbA1c, James-Todd et al. (2016) (129) did not observe a significant correlation between PIGF, belonging to the VEGF family, measured in the third trimester and baseline HbA1c or HbA1c at delivery. A significant negative correlation between the expression of visfatin and the maternal HbA1c in the third trimester in women with T1DM and LGA infants was observed as well (126). Cohen et a. (2014)

(130), who found elevated sFlt1/PIGF ratios in the group with T1DM and preeclampsia, determined a higher first trimester HbA1c in this group compared to the T1DM group without preeclampsia, who had lower sFlt1/PIGF ratios. Additionally, one study evinced an association between maternal HbA1c, measured at gestational week 22, 30 and 34 and serum concentration of FGF-2 (136).

Regarding the IGFs and PGH, the studies achieved different results. On the one hand, one study ascertained a correlation between the mean postprandial glucose and the PGH and free PGH concentrations in maternal serum in T1DM (109). On the other hand, other results showed a significant increase of PGH during an induced hypoglycemia in the third trimester in women with IDDM (158). Higgins et al. (2012) (106) did not find any significant correlation between maternal HbA1c and PGH, but found a significant correlation between fetal IGF-1 and a HbA1c >7% measured in an early state of pregnancy, but not at any other time during pregnancy. Another study observed a positive correlation between fetal IGF and maternal HbA1c as well (151). Ringholm et al. (2008) (159) measured decreased IGF levels throughout pregnancy in women who had repeated severe hypoglycemic events, compared to women with T1DM without severe hypoglycemia. The HbA1c, though, did not differ between the groups. In contrast, Bhaumick et al. (1986) (150) did not find any difference of IGF-1 levels between good or poor controlled T1DM women.

The expression of MT1-MMP protein, which was increased in first-trimester placentas in T1DM women, showed no altered response to glucose, but to insulin, IGF-2 and TNF-α (143).

7.7 Oxidative Stress and Inflammation in Placentas in T1DM

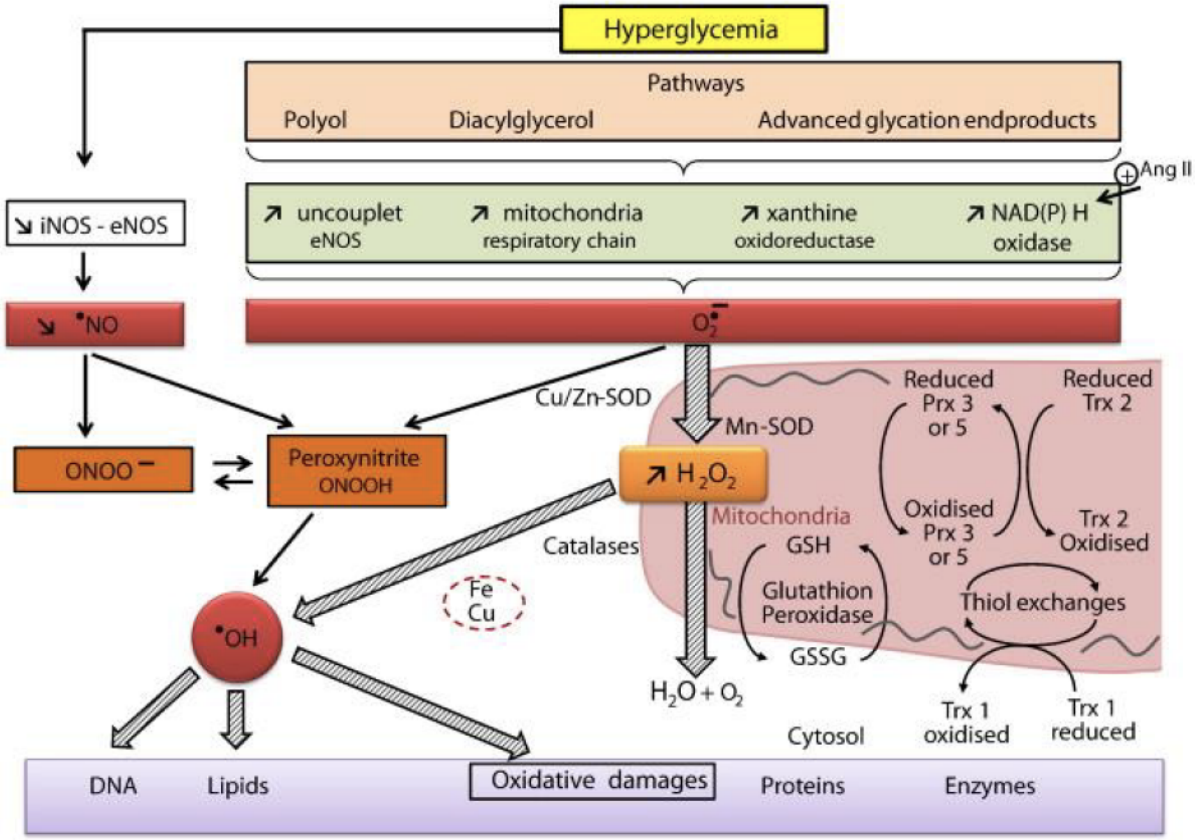
7.7.1 Oxidative Stress in T1DM

Oxidative stress is defined as *"an imbalance between oxidants and antioxidants in favour of the oxidants, potentially leading to damage"* (160). The elevated levels of reactive oxygen species (ROS), which are a byproduct of the aerobic metabolism, include hydroxyl radical (HO·), hydrogen peroxide (H_2O_2), superoxide anion radical ($O\cdot_2^-$) and further different peroxides. They lead to a damage of lipids, proteins and DNA (161, 162). In a healthy individual the homeostasis of ROS is equalized engendering a ROS level that is in stable condition. If this equilibrium gets into an imbalance, which can be due to various reasons, it

results in oxidative stress (161). Additionally, there are various subgroups of oxidative stress described by their way of occurrence (163). It would go beyond the scope of this work to explain all subgroups that describe the different causes and mechanisms leading to oxidative stress. Furthermore, the knowledge about the causes and consequences of oxidative stress grew sharply over the last decades and thus it would be too complex to discuss the pathophysiology of oxidative stress more in-depths. The emphasis of this work is on the role of oxidative stress in pregnancies complicated by T1DM.

First of all, different studies have already proven the existence of oxidative stress in T1DM. Increased plasma levels of markers for oxidative stress, such as lipid peroxidase (LPO), glutathione reductase (GR) or thiobarbituric acid reactive substances (TBARS) were often found in T1DM compared to a healthy control group (164–166). Additionally, higher values of 8-isoprotanes, another marker for oxidative stress, were found in the exhaled breath condensate in T1DM, compared to a healthy control group (167). Furthermore, a common observation was the reduced efficiency of the antioxidant defense, illustrated by a reduced plasma levels of the total antioxidant capacity (TAOC), reduced glutathione (GSH), glutathione peroxidase (GPx) or catalase (164–166, 168). The manifestation of oxidative stress in T1DM seems to correlate with the glycemic control, either with the HbA1c or with a glycemic variability (164, 165). This was confirmed by the study of Cariello et al. (2016) (169). They observed a reduction of the plasma 8-isoprostaglandin F2α levels in a normoglycemic state compared with an infusion of glucagon-like peptide-1 (GLP-1) and further a normalized endothelial function. This is one of the main problems in T1DM or rather diabetes in general. The non-enzymatic glycation of proteins, the glucose oxidation and lipid peroxidation result in the generation of free radicals. This leads to endothelial dysfunction and thus to the common known vascular complications in diabetes (170). Figure 8 was extracted from the work of Rochette et al. (2014) (171). It demonstrates the different pathways that can lead to oxidative stress induced by hyperglycemia in diabetic patients and thus to cellular damage and further to vascular complications.

Figure 6 "Schematic representation of glucose metabolism and oxidative stress coupled to three major pathways: polyol, diacyglycerol and AGE" extracted from Rochette et al. (2014) (171)



"Radicals derived from oxygen: $O_2\bullet^-$, superoxide; •OH, hydroxyl; nitric oxide: •NO. Main antioxidant enzymes: CAT, catalase; Cu-SOD, copper SOD; Mn-SOD, manganese SOD; GPx, glutathione peroxidase; GR, glutathione reductase; GSH, glutathione; GSSG, GSH disulfide; H_2O_2, hydrogen peroxide; HO-1, heme oxygenase-1; NAD(P)H, nicotinamide adenine dinucleotide phosphate; eNOS: endothelial nitric oxide synthase; iNOS: inducible nitric oxide synthase; peroxynitrite: $ONOO^-$/ONOOH: Trx, thioredoxin; Prx, peroxiredoxin" (171)

7.7.2 Oxidative Stress in T1DM Placentas

The existence of oxidative stress in T1DM indicates that oxidative stress is implicated in pregnancies complicated by T1DM as well and that it may affect placental and fetal development. Increased levels of TBARS, LPO, catalase or malondialdehyde (MDA), found in maternal plasma either during pregnancy (172, 173) or in maternal and fetal plasma during labor or after delivery (174–176) in pregnancies with T1DM, IDDM or PGDM, substantiates the presumption of oxidative stress in diabetic pregnancies. The results of Peuchant et al. (2004) (172) showed a significant positive correlation between the maternal HbA1c and the maternal plasma level of erythrocyte-free MDA in T1DM. Apart from that, the studies observed some differences regarding the levels of Superoxide-Dismutase (SOD). Most studies found decreased levels measured in maternal plasma during gestation or at delivery

or in cord blood (172, 173, 175, 176). But two studies found significantly elevated levels of SOD or an increased activity in erythrocytes in maternal blood (174, 177). In addition, a further discrepancy emerged. Some observed decreased levels of GPx, GSH or the total antioxidative capacity (TAOC) in maternal plasma (172, 174), others found increased levels of GPx or GPx activity in erythrocytes and GSH in maternal plasma or in the fetal cord blood (174–177). All results measured from T1DM, IDDM or PGDM were compared to healthy control cases.

The evidence of oxidative stress in T1DM pregnancies, measured by markers of oxidative stress in plasma of mothers and infants, raises the question if and how the placenta is influenced by oxidative stress and whether it could play a role in the development of the known complications in T1DM. Placental oxidative stress has been described as a leading cause in the emergence of preeclampsia, IUGR and spontaneous abortion, which are complication that can occur in a diabetic pregnancy as well (178, 179). Placental tissues of T1DM mothers revealed the presence of oxidative stress. Elevated marker levels of oxidative damage, for example MDA or protein carbonyls were found in the term placenta (176, 180). Heat shock protein 70 (HSP70) or heme oxygenase 1 (HO-1) were elevated in the first trimester placenta in T1DM (181). Markers of the antioxidant defense indicate the attempt of the placenta to counteract oxidative stress, displayed by an increased activity of GPx and SOD3 and higher levels of reduced glutathione and lower levels of oxidized glutathione (180, 181). In contrast Johnston et al. (2016) (182) supplemented Vitamin C and E to pregnant women with T1DM to find out whether it could affect the placental antioxidant defense and thus reduce placental oxidative stress, but they did not observe a significant effect.

Additionally, higher values of H_2O_2, a mitochondrial ROS, and a decreased activity of the electron transport chain (ETC) complex imply dysfunctional placental mitochondria in T1DM (183). Nitrotyrosine residues (NT), another indicator for placental oxidative stress, was localized in villous stroma and vascular endothelium (184). NT is nitrated in proteins through peroxynitrite and it can lead to loss of function of proteins and can cause cell damage (185). Stanek et al. (2001) (186) examined placentas in cases of perinatal mortality, either caused by preeclampsia or IDDM. They observed that a higher intensity of NT positively correlated with the amount of ECM. Furthermore, a higher oxygen diffusive conductance, observed in diabetic placentas is a further evidence for a hypoxic environment in the diabetic placentas, mainly located on the fetal placental site (187).

The previous results reveal that the placenta in T1DM is affected by oxidative stress and this can lead to disruption of the placental development and function. Placental hypoxia induces the response of HIF-1, which regulates the expression of VEGF and EPO to ensure fetal oxygen supply. But HIF-1 can further facilitate a mitochondrial autophagy and therefore reduce the occurrence of mitochondria in the placenta. It can enhance cytotrophoblast proliferation but inhibits its differentiation and invasion. Oxidative stress leads to HIF-1 stabilization intracellular which can rise the glycolytic flux to provide ATP generation anaerobically (178, 188). The expression of HIF-1 can not only be stimulated by hypoxia but by hyperglycemia and ROS itself (178, 189). The recently published paper of Mitsui et al. (2018) (189) examined the expression of HIF-1 mRNA in the placenta in hyperglycemia *in vitro*. The expression of HIF-1 mRNA was significantly increased after 24 hours culture under hyperglycemic condition compared to a normal glucose control group, so were the mRNA expression of sFlt-1, PIGF and VEGF.

The production of ROS in the placenta can be triggered by hyperglycemia as well, independent of the oxygen level (190). High levels of placental ROS can lead to endothelial dysfunction, trophoblast apoptosis or a dysfunctional cellular metabolism. It can further release pro-inflammatory cytokines and anti-angiogenic factors (178, 191). Oxidative stress appears in a physiologic pregnancy as well. This is caused by the increasing fetal metabolic demands which leads to an elevated placental oxygen level with an enhanced ETC activity and further to the formation of ROS (192). At the end of the first trimester the maternal circulation develops resulting in an increase of oxygen tension. Hence, oxidative stress in the trophoblast occurs (193). Burton et al. (2017) (191) also observed a rise of trophoblastic stress towards the end of gestation. In a normal pregnancy the placenta can prevent itself from excessive oxidative stress by its antioxidant defense system. It converts ROS to water and molecular oxygen (190). If oxidative stress is prevalent it can cause placental damage. Severe trophoblastic stress can cause a reduction of protein synthesis and a secretion of cytokines (191). Furthermore, the fusion of cytotrophoblast into syncytiotrophoblast can be restricted by elevated levels of SOD, coming along with reduced expression of hCG, hPL and PGH (178).

Pereira et al. (2015) (192) examined six transcription factors that link oxidative stress with trophoblast invasion and the development of placental vasculature. The expression of E26 transformation specific oncogene homolog 1 (Ets-1) is heightened by hypoxia, ROS or HIF-1. It can enhance VEGF expression. Krüppel-like factor 8 (KLF-8) is involved in cellular differentiation and angiogenesis. Nuclear factor kappa-light-chain-enhancer of

activated B (NF-κB) can be upregulated by ROS or VEGF and it upregulates VEGFR-2 and the expression of cytokines. A10-fold increase was observed in preeclampsia. NF-E2-related factor 2 (Nrf 2) is associated with the nonmitochondrial antioxidant defense. It is enhanced in extravillous trophoblast in the early placenta in IUGR and preeclampsia. The specificity protein 1 and 3 is involved in the signal path from oxidative stress to the elevated expression of VEGF. It further seems to influence the expression of tissue inhibitors of metalloproteinase-2 (TIMP-2) which regulates the activity of MMP and therefore trophoblast invasion and spiral artery remodeling. At least the signal transducer and activator of transcription 3 (STAT-3) seems to react to reactive nitrogen species and regulates cellular mechanisms regarding the influence of cytokines and growth factors, for example the expression of VEGF or the secretion of MMP-2 or MMP-9. STAT-3 is further upregulated through enhanced phosphorylation by TNF-α. All these transcription factors seem to interact with different factors and conditions that appear in T1DM as well.

In diabetes another mechanism leads to placental vascular dysfunction. The auto-oxidation of glucose generates free radical hydroxylic anions, surpassing the antioxidant defense, and results in a more vulnerable endothelium towards free radicals. NO and free radicals react to form peroxynitrite which has a high ability to cause cellular damage. Long-term hyperglycemia can form advanced glycation products (AGE). If AGE bind to its receptor it can activate the expression of NF-κB and cytokines (194). Additionally, studies have found an attenuated placenta vascular reaction towards vasoconstrictors and vasodilators in diabetes and preeclampsia compared to a healthy control group after the treatment with peroxynitrite (195, 196). One study found an even more decreased response towards vasodilators in IDDM than in preeclampsia, whereas the response to vasoconstrictors was reduced similarly in these groups. NT is found in vessels of diabetic placentas. It is a marker of peroxynitrite activity and therefore indicates vascular dysfunction in diabetic placentas due to oxidative and nitrative stress. Additionally, Bisseling et al. (2005) (197) observed an impaired vasodilatation effect of the cyclooxygenase pathway in T1DM. Indomethacin functions as a cyclooxygenase inhibitor. The increased pressure generated by indomethacin, starting with a similar baseline pressure, was significantly reduced in the diabetes group compared to control.

7.7.3 Inflammation in T1DM Placentas

Inflammation and oxidative stress in the diabetic placenta are closely linked. It has been mentioned in the previous paragraph that oxidative stress can stimulate the release of cytokines. Placental cytokines such as TNF-α, leptin or IL-6 are released by Natural killer cells (NK-cells), Hofbauer cells (placental macrophages), syncytiotrophoblast or cytotrophoblast (198). There are many more cytokines, but it would be beyond the scope of this work to discuss more of them. Elevated levels of TNF-α, leptin and IL-6 in T1DM were demonstrated in different studies (33, 143). TNF-α activates trophoblast apoptosis in term placentas and can inhibit placental invasion. TNF-α and leptin can stimulate the gene expression and activity of MMP in cytotrophoblast and furthermore trigger the release of inflammatory markers or vascular remodeling. The pro-inflammatory milieu can additionally lead to remodeling of ECM in the early stages of placental and fetal development (198–200). Elevated levels of CRP and LDL cholesterol in umbilical-cord serum of T1DM infants complement the assumption of inflammation in T1DM (201). Du et al. (2013) (202) found even more increased levels of inflammatory markers like CRP in T1DM mother who developed preeclampsia compared to T1DM mothers without preeclampsia indicating that inflammation could take part in the development of preeclampsia in T1DM.

The early healthy placenta consists of 30-40% leukocytes, these are uterine NK cells (uNK cells), macrophages and T-lymphocytes. Uterine NK cells are the most dominant leukocytes in the early placenta. It has been suggested that they have an impact on trophoblast invasion and spiral artery remodeling. They seem to produce cytokines, growth factors and even angiogenic factors like VEGF or PIGF. Uterine macrophages imply an involvement in placental inflammation, spiral artery remodeling and trophoblast invasion. The subgroup M1 appears to be microbicidal and pro-inflammatory, whereas the subgroup M2 seems to have an immunomodulating, thus anti-inflammatory effect responding to inflammation. They were further found to release cytokines and factors regulating angiogenesis and tissue remodeling (203, 204).

The study of Sisino et al. (2013) (204) showed that in a hyperglycemic environment Hofbauer cells shifted from a M2 to M1 profile. The markers for M1 macrophages were expressed significantly higher. The ratio of a marker for M2 and one for M1 (CD163/CD68) was significantly decreased in T1DM. These results were found in isolated Hofbauer cells from rats *in vitro* and in T1DM human placentas *in vivo*. Furthermore, a significantly

increased monocyte adhesion to decidual endothelial cells was observed in T1DM placentas (205, 206). One study found a positive association between the augmented monocyte adhesion and the expression of intercellular adhesion molecule-1 (ICAM-1), but not vascular cell adhesion molecule-1(VCAM-1) in T1DM. These molecules are integrins mediating the binding of monocytes to endothelial cells. After the pretreatment of decidual endothelial cells with the cytokine IL-1β or AGE, homocysteine or glucose, the expression of ICAM-1 increased in response in normal and T1DM placentas. These results suggest a stimulation of ICAM-1 by pro-atherogenic or pro-inflammatory factors leading to an increased monocyte adhesion and thus inflammation and vascular dysfunction in T1DM placentas (206). Szukiewicz et al. (2013) (207) found increased levels of Fraktalkine (CX3CL1) and its receptor (CX3CR1R) in White Class C diabetic placentas combined with a higher density of placental micro vessels. Fraktalkine is a chemokine involved in processes like angiogenesis, inflammation, extravillous trophoblast invasion and the interactions of villi and circulating maternal cells. Fraktalkine can be stimulated by hypoxia or cytokines, for example TNF-α or IL-1β (207, 208).

7.7.4 Oxidative Stress and Inflammation Depending on Maternal HbA1c

This work emphasizes on the impact of the maternal HbA1c value in T1DM on the human placenta. Some results have stated an association between maternal serum markers for oxidative stress and HbA1c or glycemic varieties. But no studies were found that investigated placental oxidative stress and inflammation depending on the maternal glycemic control.

8. Discussion

8.1 Development of Placental Weight in T1DM

The placental weight has a great impact on birth weight and the newborn's health. It does not only influence the development of the fetus during pregnancy or the perinatal outcome, but can increase the risk for cardiovascular diseases in their adult life. It is not clearly evinced whether a higher placental weight increases this risk per se or if the underlying mechanisms leading to a higher placental weight increase the risk for cardiovascular diseases. The results further show that placentas from T1DM women are heavier compared to placentas from

healthy women. The aim of this work was to show the development of placental weight from women with T1DM. Between the years 1964 and 2017 there was a steady fluctuation, but with a tendency to heavier placentas until 2010. The highest estimated mean value was found for the decade between 2001 and 2010. From 2011 till 2017 the mean value dropped again with a decrease of more than 100 grams. This enormous decrease can be due to various study types or the highest number of investigated placentas during this time period. This hypothesis would need further evidence. The calculated values for the time period between 1960-1990 and 1991-2017 demonstrated a decrease in placental weight as well.

The therapy for T1DM developed towards a tighter glycemic control and care during pregnancy has improved over the decades. This improvement is reflected by the positive development in reduction of the miscarriage rate as well as the perinatal mortality and outcome. The fluctuations of the placental weight in T1DM could be explained by various reasons. First, there were lack of data for the early years. Only one study was found for each of the decades 1960-1970, 1971-1980 and 1981-1990. Furthermore, maternal comorbidities, BMI or smoking habits were not taken into consideration. The prevalence of overweight or obese women, even women with T1DM increased over the last decades (209, 210). This could be an additional factor influencing the placental weight. It would be necessary to determine the influence of maternal BMI by looking at the development of placental weight in comparison to the development of maternal BMI over the years in a healthy control group. This would have been beyond the scope of this work.

A representation of the development of maternal HbA1c would have been a possibility to display the correlation between the temporal changes of placental weight and the HbA1c. The first HbA1c value in connection with placental studies was reported for the year 1987. Apart from this, the studies used different time points for the measurement during gestation, some mentioned an average HbA1c, others measured values at each trimester. Hence, no reliable conclusion could be made.

8.2 Placental Structure Depending on Maternal HbA1c

A total number of 30 studies were included in this work, 21 of these were already mentioned by the systemic review of Huynh et al. (2015) (53). The studies were categorized according to the average maternal HbA1c during gestation and were differentiated into three different groups. The first group with a HbA1c value ≤6.0% was classified as excellent glycemic

control, values between 6.1% and 7% as good control and >7% as non-optimal glycemic control. Studies in which the exact HbA1c was unknow were categorized as not specified. Some studies did not only mention an average HbA1c for all women in sum but mentioned the HbA1c value for each woman. Therefore, these studies were ranked in more than one group regarding the maternal HbA1c. For the sake of clarity, placental histopathologic alterations were divided into three groups (villous maturation, placental vasculature and intervillous space). Furthermore, different study types, analytical methods and diagnostic criteria, inclusion and exclusion criteria were integrated in this work to extend the number of studies included with the aim of analyzing the correlation between maternal HbA1c value and placental histopathology in T1DM. This could probably engender potential bias because of a great variability in the conduction of studies.

8.2.1 Villous Maturation

Altered villous maturation, especially villous immaturity was found in all HbA1c groups but just one trial observed villous immaturity in the excellent controlled group. It is worth mentioning that maturation disorders can affect all villous parts and different designations and synonyms are used to describe them. Turowski and Vogel (2018) (211) described the villous maturation disorders in diabetes mainly as an *'arrest of villous maturation'* characterized by disturbed branching of immature intermediate villi. It mainly appears during the early stages of placental development. Delayed villous maturation is further associated with prenatal or intrapartum intrauterine death (212). Hence, villous maturation disorders can lead to disturbance in placental development.

8.2.2 Placental Vasculature

Vascular abnormalities in T1DM human placentas were the most common findings in all groups, except the non-optimal controlled group. In the non-optimal controlled group vascular abnormalities and altered intervillous space were observed in an equal number of studies. The excellent controlled group contained the fewest number of studies with significant altered placental vascularization. Vascular abnormalities included hypo- and hypervascular villi, and increased capillary volume and surface area, increased surface area of terminal and immature intermediate villi. Additionally, chorangiosis, defined as an

enhanced terminal villus vascularization (211), thickening of trophoblast and capillary basement membrane were included in vascular alterations due to reasons of clarity. All these pathologies indicate a dysfunctional placental microvascularization. The hypoxic environment in the fetal circulation can be one reason for the numerous capillaries and thus the small amount of stroma in hypervascular villi as an adaptive response (33, 46).

8.2.3 Intervillous Space

An increased absolute and relative volume of the intervillous space was the main observation in all three groups with a noted HbA1c value. This was particularly observed in placentas of macrosomia. One study in the excellent controlled group described an increased distance between the intervillous space and fetal capillaries. In contrast, in the group with an unspecified glycemic control, a reduced intervillous volume was noted more commonly but also a higher incidence of intervillous thrombi was described. These results are compatible with the villous immaturity and altered structure of terminal villi (33).

8.2.4 The Impact of First, Second and Third Trimester HbA1c

It was shown that an increased first trimester HbA1c correlated with complications like a higher birth weight, risk for macrosomia, greater incidence of fetal malformations, risk for spontaneous abortion or adverse pregnancy outcome. The pre-conceptional HbA1c seems to play a role alike. Higher values were associated with a higher birthweight and an increased risk for adverse pregnancy outcome. In contrast a correlation between third trimester HbA1c and the risk for macrosomia or LGA infants was observed in some studies as well.

Establishing a similar association between the first trimester maternal HbA1c and placental morphology proved to be more difficult. All studies covered in this work found significant histopathologic changes. In addition, the women had a significantly higher first trimester HbA1c compared to the second and third in all studies. Most studies did not analyze the correlation between the maternal HbA1c and placental changes because their focus was different. The studies that investigated a correlation showed divergent results regarding the maternal HbA1c at a specific time period and placental histopathologies. But it can still be suggested that the first trimester or pre-conceptional HbA1c has a greater impact on the placenta than the HbA1c at a later point during gestation. It is noteworthy though that

hitherto no studies were published analyzing the correlation of pre-conceptional HbA1c and placental morphology. Therefore, this needs to be investigated. In all studies included in this work, a significant higher HbA1c value in the first trimester was found compared to the second and third trimester. Thus, it is probably of an importance for women with T1DM to plan their pregnancies to improve their glycemic control already prior to conception. A paper published by Pearson et al. (2006) (213) showed that women with T1DM who achieved their target HbA1c value before interrupting contraception had the lowest rate of adverse pregnancy outcome. Improving the glycemic control prior to conception could also reduce the known placental changes in T1DM. Therefore, studies that investigate the impact of a pre-conceptional optimal controlled T1DM on the placenta are needed.

8.2.4 The Significance of Maternal HbA1c in Pregnancies Complicated by T1DM

The evaluation of the different studies dealing with placental histopathologic alterations in women with T1DM showed that it is difficult to establish an accurate correlation between maternal glycemic control and the extent of placental pathologies. It seems that an excellent glycemic control, defined by a HbA1c value ≤6%, can minimize placental alterations. This group encompassed the fewest morphologic findings compared to the good, non-optimal controlled and the group with an unreported HbA1c. This group contained the fewest number of studies, though. These results raise the question whether the maternal HbA1c is a key determinant for placental and fetal development. One possibility would be that already brief hypo- or hyperglycemic episodes, without an increased HbA1c, can affect the placenta. The results of Björk and Persson (1982) (56) support this hypothesis. They showed a correlation between an increased MODD between the gestational week 12 and 32 and placental changes.

Kyne-Grzebalski et al (1999) (214) had six women with T1DM measured their blood glucose at home. Although all women were classified as well controlled, regarding their HbA1c, 42 to 68% of the pre-prandial measured values were above the intended range. Additionally, further studies showed reduced numbers for preeclampsia, caesarian section and birth weight >90th percentile in a group with tight-moderate controlled fasting blood glucose compared to a group with a loose control (215). Three intraperitoneal glucose injections in rats in the early pregnancy increased the placental and fetal weight. In human pregnancies higher glucose variations and changes between 180 days of gestation and birth increased the risk for LGA infants (216, 217). Significant stronger associations between glucose measures and birth weight, sum of skinfolds and percent body fat >90th percentile

were found in comparison to the HbA1c. But it revealed similar odd ratios for C-section, preeclampsia and preterm delivery (218). It seems that the maternal HbA1c is not the only conclusive parameter to define the glycemic control during pregnancy, but transient hyperglycemia can have an effect as well. The HbA1c value is a good parameter for a long-term monitoring in diabetes in general, but the average HbA1c during pregnancy does not seem to be a reliable predictor for placental structural changes.

In sum, the care for women with T1DM still poses a challenge to the responsible doctors. Even a well-controlled diabetes, regarding maternal HbA1c, does not prevent the placenta or the fetus from all possible complications.

8.3 The Effect of the Fetal Sex

Studies showed a worse perinatal outcome in male neonates compared to females even in healthy pregnancies. The male sex was found to be an independent risk factor for stillbirth and was associated with a higher birthweight. Almost all adverse pregnancy outcomes were more frequent in male newborns. In male infants from T1DM mothers, congenital malformations, preterm delivery and respiratory disorders were more common.

Regarding placental alterations in T1DM, males had more severe placental dysfunction and a higher BW/PW ratio. Only one study was found that investigated the effect of the fetal sex on the placental histopathology in T1DM. Placentas from male fetuses had increased fetal capillary volume and surface area. A higher distance across the stroma and a greater diameter of capillaries were observed additionally (40). The underlying causes are not fully understood, yet. A recently published paper by Gonzalez et al. (2018) (219) analyzed the first trimester placenta transcriptome in male and female fetuses in non-diabetic pregnancies. The male infants were significantly heavier at birth. Furthermore, they identified 112 genes that differed significantly between the two groups. It would be beyond the scope of this work to discuss all the differences, but genes that are associated with metabolism were upregulated in the placentas of male fetuses. They were implicated in nutrient deficiency responses. All these altered gene expressions could be one reason for the differences in placental function or growth and can lead to different complications during pregnancy. Thus, it can probably cause different reactions towards a stressful environment in T1DM, but further studies are needed to clarify the hypothesis.

8.4 Placental Angiogenesis in T1DM

8.4.1 Angiogenic Factors in T1DM

The investigated angiogenic factors in placentas from T1DM women were all altered compared to placentas from healthy gravidae. VEGF, expressed by the syncytiotrophoblast in the terminal villi, promotes angiogenic remodeling and induced the development of a placental capillary network. It was increased in all studies in T1DM. VEGF itself can be stimulated by HIF-1 or PBEF, markers which were increased in T1DM as well. Insulin can stimulate the expression of VEGF through the activation of eNOS, which further activates HIF-1. PIGF is in involved in the branched angiogenesis as well. Elevated levels were found at the end of gestation. It correlated with birth weight and was associated with a higher risk for macrosomia. But no differences occurred during the early pregnancy. This indicates its potential role at the end of gestation, leading to heavier placentas. Additionally, an increased sFlt1/PIGF ratio was especially observed in T1DM with preeclampsia. A higher intensity of FGF2 in the syncytiotrophoblast and villous stroma was common in T1DM as well. It takes part in cell proliferation, migration, cell-cell interaction and reduces ECM. The increase of IGF-1 was closely linked to the increase of PGH in the third trimester. IGF-1 has a metabolic, mitogenic effect. PGH does not influence placental angiogenesis directly, but affects maternal metabolism by increasing the gluconeogenesis, lipolysis and the stimulation of IGF-1 expression. They seem to affect the neonate's birth weight and placental weight.

The increase of different angiogenic factors could be the molecular explanation for the demonstrated increase in angiogenesis reflected by longer vessels in T1DM placentas. This can lead to heavier placental weights and placental dysfunction. The augmented angiogenesis seems to be a placental adjustment mechanism for adapting to the increased fetal oxygen demand caused by fetal hyperinsulinemia.

8.4.1 Angiogenesis and HbA1c

The results regarding the role of the maternal HbA1c in angiogenesis differed between the studies. Some results showed a correlation between the mean HbA1c or fasting blood glucose levels and VEGF. Other studies found a correlation just between the third trimester HbA1c and VEGF. Further correlations were observed between the sFlt1/PIGF ratio and the first trimester HbA1c. Higher FGF values were associated with an increased HbA1c at

gestational week 22, 30 and 34. The PGH correlated with post-prandial glucose levels, but also with induced hypoglycemia in the third trimester. IGF-1 showed a positive association with increased HbA1c values in the early pregnancy and was decreased in T1DM women who had repeated hypoglycemic events, without an altered HbA1c.

These results preclude to draw a conclusion regarding the effect of the maternal HbA1c on the placental angiogenesis. The first trimester seems to play a more important role than the second or third, comparable to the results mentioned in the paragraph 7.4.5. Furthermore, brief hyper- or even hypoglycemic events may have the potential to affect the expression of angiogenic factors, even with normal HbA1c values. No studies were found dealing with the peri-conceptional HbA1c and its effect on placental angiogenesis. This emphasizes the need of studies analyzing the effect of the glycemic control in the early stages of pregnancy in T1DM.

8.5 Oxidative Stress and Inflammation in Placentas in T1DM

The existence of oxidative stress in T1DM in general could already be demonstrated by increased levels of oxidative stress markers. Its manifestation correlated with the HbA1c value or the glycemic variability in some studies. In pregnant T1DM women some markers for oxidative stress were increased in the early pregnancy in maternal serum, others were elevated in maternal and fetal cord plasma during delivery and after birth. A correlation to the maternal HbA1c could be observed for one marker, the erythrocyte-free MDA. Regarding the antioxidant defense systems in pregnant T1DM women, the results differed. Most studies measured decreased SOD levels. Maternal plasma levels from other antioxidants were increased or decreased as well.

Tissue samples from T1DM placentas revealed elevated markers for oxidative stress as well. This demonstrates the existence of oxidative stress in the human T1DM placenta as well as in non-diabetic pregnancies. However, effective antioxidant defense systems may prevent damage in the healthy placenta. In T1DM placentas antioxidants were increased. This could indicate an attempt to counteract oxidative stress in the placenta. Furthermore, NT was detected in villous stroma and vascular endothelium. It is a marker for peroxynitrite activity and implicates vascular dysfunction. An increased oxygen diffusive conductance in the diabetic placenta signifies an attempt to compensate fetal hypoxia. Hypoxia induces the release of HIF-1, which itself stimulates the expression of VEGF and EPO. It further

stimulates cytotrophoblast proliferation but inhibits its differentiation and invasion. In addition, hypoxia can lead to intracellular HIF-1 stabilization, which in turn increases placental glycolytic flux. These mechanisms seem to balance the increased fetal oxygen demand and underlines the vascular dysfunction in T1DM placentas. Hyperglycemia can trigger ROS production and can stimulate HIF-1 itself. ROS cause endothelial dysfunction, trophoblast apoptosis or release of pro-inflammatory cytokines.

It is unclear whether brief hyperglycemic events, with a HbA1c in the normal range, can cause placental oxidative stress. Vascular alterations appeared in excellent controlled T1DM already, defined by HbA1c values ≤6%. Thus, brief hyperglycemic events would be a possible cause. One study analyzed different placental transcription factors that are involved in angiogenesis, trophoblast invasion, secretion of cytokines or MMPs. They can be activated or upregulated by hypoxia, HIF-1, ROS, VEGF or TNF-α. For example, NF-κB is upregulated by ROS, VEGF or AGE, that occur in diabetic patients very commonly. It stimulates VEGFR-2 expression and the release of cytokines. These indicate an altered expression of these transcription factors in T1DM placentas as well. It could be a possible cause for the vascular dysfunction in T1DM. It is known that oxidative stress is one main cause for the development of preeclampsia, IUGR or spontaneous abortion. All these complications can occur in T1DM. Hence, placental oxidative stress seems to be a very important problem in T1DM and needs further investigations.

Oxidative stress releases cytokines in T1DM placentas. One example is TNF-α, it can activate trophoblast apoptosis and inhibit placental invasion. TNF-α and leptin trigger the release of further inflammatory markers and can induce vascular remodeling. These cytokines were elevated in T1DM placentas. Moreover, a shift from an immunomodulating, anti-inflammatory (M2) profile of Hofbauer cells towards a more pro-inflammatory profile (M1) was observed in T1DM. An increased monocyte adhesion to the decidual endothelium combined with elevated levels of ICAM-1, an integrin mediating the binding of monocytes, was found in T1DM as well. Inflammation is known to play a role in the development of atherosclerosis. Thus, placental inflammation seems to take part in the development of vascular complications in T1DM alike. The infiltration of monocytes is one important mechanism in its progression.

Placental oxidative stress and inflammation seem to be a main cause in the development of enhanced placental vasculature in T1DM. It can lead to preeclampsia, IUGR and spontaneous abortion, which are complications that occur in T1DM pregnancies more frequent than in healthy gravidae. No studies were found investigating placental oxidative

stress or inflammation in relationship to the maternal HbA1c. Further studies are needed, especially investigating the effect of the first trimester HbA1c, as this seems to be the most sensitive time period leading to placental alterations.

9. Conclusion

T1DM is less common than T2DM or GDM. Thus, it has less emphasis in research. This review gives a detailed summary on the current known literature with a focus on the significance of the maternal glycemic control, specified by the HbA1c value. The glycemic control has improved over the last decades as well as the pregnancy care and fetal outcome. This work has shown that the average HbA1c seems to be less important than the first trimester HbA1c. The role of the pre-conceptional HbA1c has not been researched, yet. Hence, further studies are needed to analyze the influence of pre-conceptional HbA1c values on the placenta. Additionally, male fetuses have more complications during pregnancy and more placental abnormalities in T1DM than female fetuses. The definite cause for this difference remains unclear. It seems to be associated with different gene expressions in the placenta. Placental oxidative stress and inflammation suggest that these are the main pathomechanisms leading to vascular dysfunction and placental maldevelopment in T1DM. This work underlines the importance of a comprehensive information to women with T1DM about good pre-pregnancy care. This could reduce maternal and fetal risks for complications during pregnancy and after delivery.

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