Diploma Thesis

Modifiers of the Neonatal Insulin Level

Submitted by

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Affidavit

I declare that I wrote this thesis independently and without assistance from third parties, that I only used sources declared within the thesis and that I marked all sources, used either literally or by content, clearly.

Graz, 13.09.2018 Anna Mangge (eh)

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I want to thank my supervisor ao. Univ. – Prof. Dr. phil. Gernot Desoye for giving me the opportunity to gain insight into such an exciting and meaningful topic, for guiding me through the process of research and writing and especially for always being available and understanding.

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Abstract

The neonatal insulin level and its influence on blood glucose is an important parameter for physicians, nurses and other clinical staff to assess the neonates' metabolic functions and to diagnose and treat possible adverse outcomes like hypoglycemia and brain damage.

There is a lot of knowledge about factors modifying the neonatal insulin, c-peptide, proinsulin and split proinsulin levels but yet there is a lot research to be done. This thesis summarizes the current state of knowledge about different circumstances and diseases, parental as well as fetal and neonatal, influencing the neonatal insulin concentrations, focusing on an elevation of insulin measured in the umbilical cord blood.

Zusammenfassung

Die Menge an Insulin im Blut des Neugeborenen und sein Einfluss auf den Glucose Spiegel ist ein wichtiger Parameter für Ärzte/ Ärztinnen, PflegerInnen und weiteres klinisches Personal um Stoffwechselfunktion des Kindes unmittelbar nach der Geburt beurteilen zu können und mögiche gefährliche Entgleisungen wie Hypoglykämie und daraus resultierende Hirnschäden rechtzeitig zu erkennen und zu behandeln.

Es existiert bereits ein breites Wissen über verschiedene Faktoren, die den kindlichen Gehalt von Insulin, C-Peptid, Proinsulin und Insulin Split-Formen im nachgeburtlichen Nabelschnurblut beeinflussen. Jedoch gibt es noch einige Wissenslücken zu diesem Thema und weitere Forschung ist vonnöten um die Vorgänge im Neugeborenen zur Gänze zu verstehen.

Diese Diplomarbeit zeigt den aktuellen Stand der Wissenschaft bezüglich verschiedener Krankheiten, sowohl elterlich als auch kindlich, und anderen Einflussfaktoren auf den neonatalen Insulin Spiegel, vorzugsweise gemessen im Blut der kindlichen Nabelschnur unmittelbar nach der Geburt.

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Abbreviations

ADP _____ Adenosine Di-Phosphate
AGA _____ Average for Gestational Age
Alpha KG _____ Alpha Ketoglutaric Acid
ATP _____ Adenosine Tri-Phosphate
AVG _____ Assisted Vaginal Delivery
BMI _____ Body Mass Index
BWS _____ Beckwith-Wiedemann Syndrome
Ca^{2+} _____ Calcium
CI _____ Confidence Interval
CoA _____ Coenzyme A
CS _____ Cesarean Section
CPE _____ Carboxypeptidase
DAG _____ Diacylglycerol
DHAP _____ Dihydroxyacetonphosphate
DM1 _____ Diabetes Mellitus Type 1
DM2 _____ Diabetes Mellitus Type 2
E _____ European
EBF _____ Erythroblastosis Fetalis
ER _____ Endoplasmic Reticulum
FFA _____ Free Fatty Acid
GA _____ Gestational Age
GDM _____ Gestational Diabetes Mellitus
GLUT2 _____ Glucose Transporter Type 2
Gly3P _____ Glycerol 3-Phosphate
HIV _____ Human Immunodeficiency Virus
IAB _____ Insulin Anti-Bodies
IDDM _____ Insulin Dependent Diabetes Mellitus
IGF _____ Impaired Fasting Glucose
IGT _____ Impaired Glucose Tolerance
IRDS _____ Infant Respiratory Distress Syndrome
IUGR _____ Intra-Uterine Growth Retardation
K _____ Potassium

LGA _____Large for Gestational Age

LP_____ Born Late Preterm

NAD+ _____ Nicotinamidadeninnucleotide

NM _____Non-Diabetic Mothers

OAA _____ Oxaloacetate

OAD _____ Oral Anti-Diabetics

OGTT _____ Oral Glucose Tolerance Test

OR _____ Odds Ratio

P_____ Polynesian

PC _____ Proprotein Convertase

PCT _____Procalcitonin

PHHI _____Persistent Hyperinsulinemic Hypoglycemia of Infancy

PKC _____ Proteinkinase C

SE _____ Standard Error

SEA _____ South East Asian

SEM _____ Standard Error of Mean

SD _____Standard Deviation

SGA _____Small for Gestational Age

SP _____Signal Protein

T_____Born at Term

TCA _____ Tricarboxylic Acid

VD _____ Vaginal Delivery

VP _____ Born Very Preterm

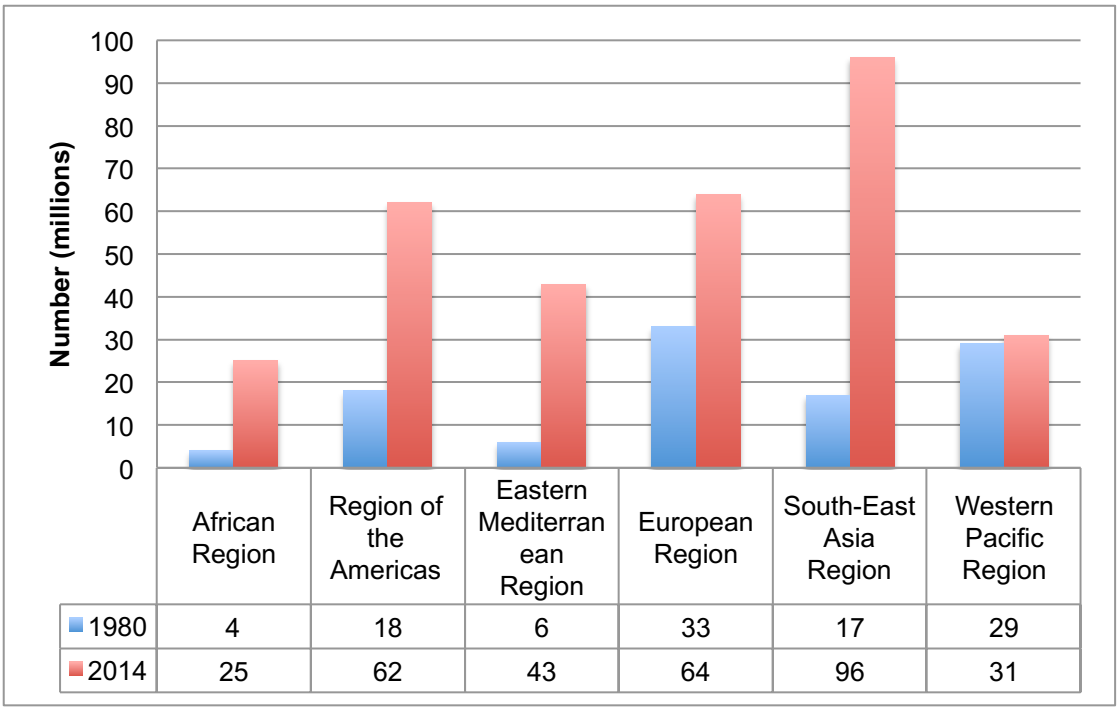
1 Introduction

1.1 The Pedersen Hypothesis

In the 1950s Jørgen Pedersen proposed: "*maternal hyperglycaemia results in foetal hyperglycaemia and, hence, in hypertrophy of foetal islet tissue with insulin-hypersecretion. This again means a greater foetal utilization of glucose. This phenomenon will explain several abnormal structures and changes found in the newborn*" (10).

Even though this hypothesis is very simplified and developed over the years, the essence of the statement is still applicable to what is seen in hospitals around the globe nowadays. In the western world type 2 diabetes and gestational diabetes reached an endemic status and more and more fertile or pregnant women are suffering from insulin resistance or obesity (4, 11).

Due to this explosion in lifestyle-associated diseases it is of great importance, not only for medical professionals, to understand those metabolic disturbances to prevent damage to next generations (Figure 1).



	African Region	Region of the Americas	Eastern Mediterranean Region	European Region	South-East Asia Region	Western Pacific Region
1980	4	18	6	33	17	29
2014	25	62	43	64	96	31

Figure 1 Estimated prevalence of diabetes in adults (≥ 18y) (4)
Pooled data from 751 population-based studies

1.2 Imbalanced Blood Glucose and Insulin Concentrations

The main aim of pancreatic hormone production is to ensure an energetic supply of the organs with glucose, especially the brain and the heart without causing damage due to a lack or an overflow of glucagon or insulin.

Diabetes mellitus is a chronic metabolic dysfunction either due to a relative or an absolute lack of insulin and the most important and frequent types are presented below (Table 1).

	Diabetes	IGT	IFG	GDM
Fasting pl. glucose	≥ 126mg/dl	< 126mg/dl	110-125mg/dl	92-125mg/dl
1-h plasma glucose**	-	-	-	**or** ≥ 180mg/dl
2-h plasma glucose*	**or** ≥ 200mg/dl	**and** ≥ 140-199mg/dl	**and** **(if measured)** < 140mg/dl	**or** 153-199mg/dl
HbA1c	**or** ≥ 6.9%	-	-	-

Table 1 Diagnostic criteria for diabetes and hyperglycemia according to the World Health Organization (12)
IGT = impaired glucose tolerance, IFG = impaired fasting glucose, GDM = gestational diabetes mellitus, pl. = plasma; * venous plasma glucose 2h after ingestion of 75g oral glucose load, ** venous plasma glucose 1h after ingestion of 75g oral glucose load

1.2.1 Diabetes Type 1

Type 1 diabetes (DM1) or insulin dependent diabetes (IDDM) is characterized by a dysfunction of pancreatic β-cells and a disability to produce enough insulin to maintain normoglycemia. B-cells are attacked and destroyed by the immune system due to a viral infection and an autoimmune reaction resulting in an absolute lack of insulin with the need of life-long insulin substitution.

Complications that are found in DM1 are either treatment induced hypoglycemia, which leads to a malnutrition of the brain and subsequent coma or hyperglycemia, which can also lead to coma, characterized by ketoacidosis and electrolyte imbalance (13).

1.2.2 Diabetes Type 2

In type 2 diabetes (DM2) or lifestyle diabetes the problem is a relative lack of insulin due to various causes that are not entirely understood. The pathogenesis includes an insulin receptor dysfunction causing peripheral insulin resistance and a secretion error leading to lower amounts of secreted insulin.

Underlying causes for developing this disease are adiposity, a high fat and high sugar diet and a sedentary lifestyle. Therapy consists of weight loss, lifestyle change and, if necessary, oral anti-diabetics and insulin.

Chronic hyperglycemia, both in DM1 and DM2, leads to a damage of especially the small blood vessels of the retina, the kidney glomerula and others. Furthermore patients are more prone to neurologic damage and arteriosclerosis, also of the bigger vessels.

1.2.3 Gestational Diabetes

The third important type, especially concerning pregnancy and childbirth, is gestational diabetes mellitus (GDM). The pathomechanism of this condition bases in the appearance of placental hormones like human placental lactogen and human chorionic gonadotrophin. At about week 20, those hormones induce maternal insulin resistance where the serum insulin concentration is increased 3 to 5 fold but the mother still develops hyperglycemia. This physiologic metabolic state is seen in every pregnant woman but if the insulin resistance gets too severe for the body to tolerate it, it becomes a problem (28). Consequences of this metabolic state are shown in Figure 2.

The management depends on the severity of the insulin resistance and consists of diet, exercise and insulin and even though GDM is often thought of a temporary disease, ending with childbirth, 50% of GDM women develop overt diabetes after pregnancy (14).

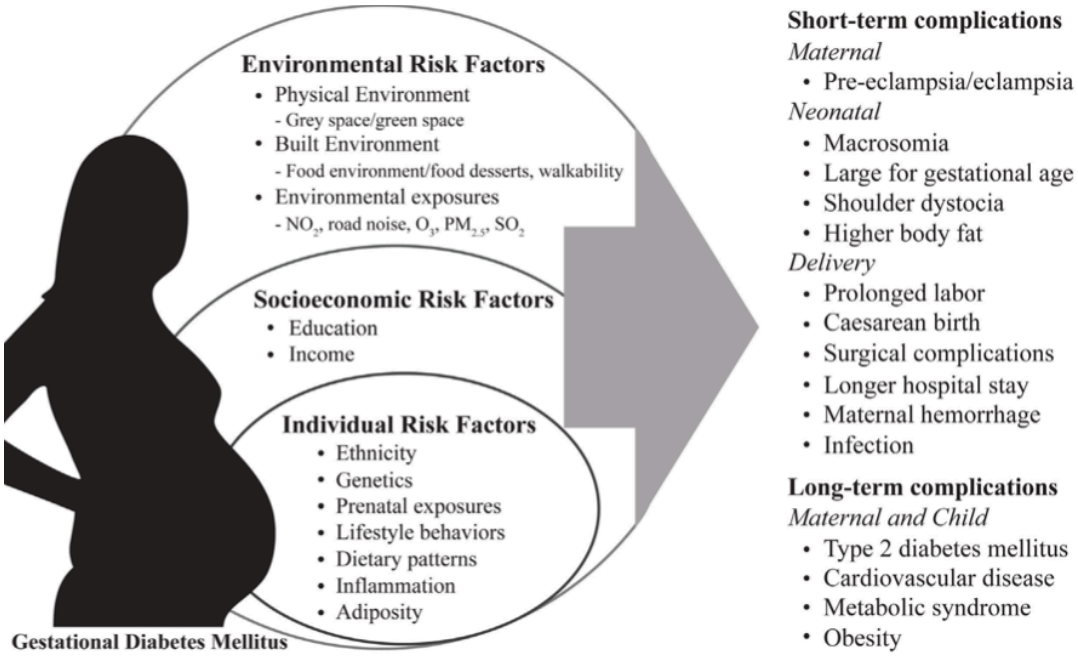


Figure 2 Maternal causes of gestational diabetes and its potential risks (15)
NO_2 = nitrogen dioxide, O_3 = ozone, $PM_{2,5}$ = particulate matter, SO_2 = sulfur dioxide

1.3 The Fetal Pancreas and the Role of Insulin

The human pancreas consists of endodermal cells and by approximately 10 weeks all endocrine cell lines are present and the organ starts to produce insulin (16-18).

In the prenatal period insulin mainly acts as a growth mediator to ensure normal fetal growth rather than a blood glucose stabilizer (19). Because fetal insulin is insensitive to the amount of fetal serum glucose (18), the blood sugar is maintained at 36 to 100 mg/dl by a steady flux of glucose from the mother to the fetus (20, 21).

As the insulin secretion in the fetus is only slightly induced by glucose, other substrates are thought to be the main stimulants of fetal pancreatic insulin secretion *in utero. In vitro* experiments with mixtures of different amino acids and adenosine mono-phosphate show an increase in insulin secretion (22). Furthermore there is an elevation in amniotic fluid amino acid concentrations in gestational diabetic mothers (23), suggesting that a high amount of amino acids is at least partly responsible for an exaggerated release of fetal insulin and the high cord insulin values seen in neonates after birth. Especially arginine is suspected to

have an impact on the fetal pancreatic β-cells, but experiments in fetal sheep showed that the effect only leads to a relevant over-production of insulin in combination with hyperglycemia (24). Another animal study with fetal pigs furthermore suggests that the insulin secretion *in utero* also depends on the amount of stored lipids and free fatty acids (25).

1.3.1 The Perinatal and Postnatal Period

At the moment the umbilical cord is cut, the neonate looses its connection to the mother and also all her aiding and metabolically stabilizing functions. The neonatal blood glucose, which until then had been provided by the mother, drops and the newborn needs to initiate glucose production on its own, which can take up to several hours (26). Furthermore neonatal glucocorticoids are no longer metabolized by the placenta causing a tremendous increase of epinephrine in the fetal blood and a subsequent drop of insulin (27).

Carrying all those very sensitive and interference-prone processes in mind it gets more obvious that only a small change in one regulating factor can have dramatic effects on the vulnerable neonate.

1.3.2 Insulin Production and Secretion

Pancreatic β-cells are responsible for the production of insulin. The precursor molecule proinsulin consists of a α-chain with 21 amino acids and a β-chain with 30 amino acids and a c-chain, which is split off forming insulin and C-peptide (Figure 3) (1).

Both molecules are secreted in equimolar amounts and about 15% of the insulin remains proinsulin and is also released from the pancreas into the blood. Besides those three markers of pancreatic function, the split form of proinsulin, 32-33 split proinsulin, is also detectable in the blood (28).

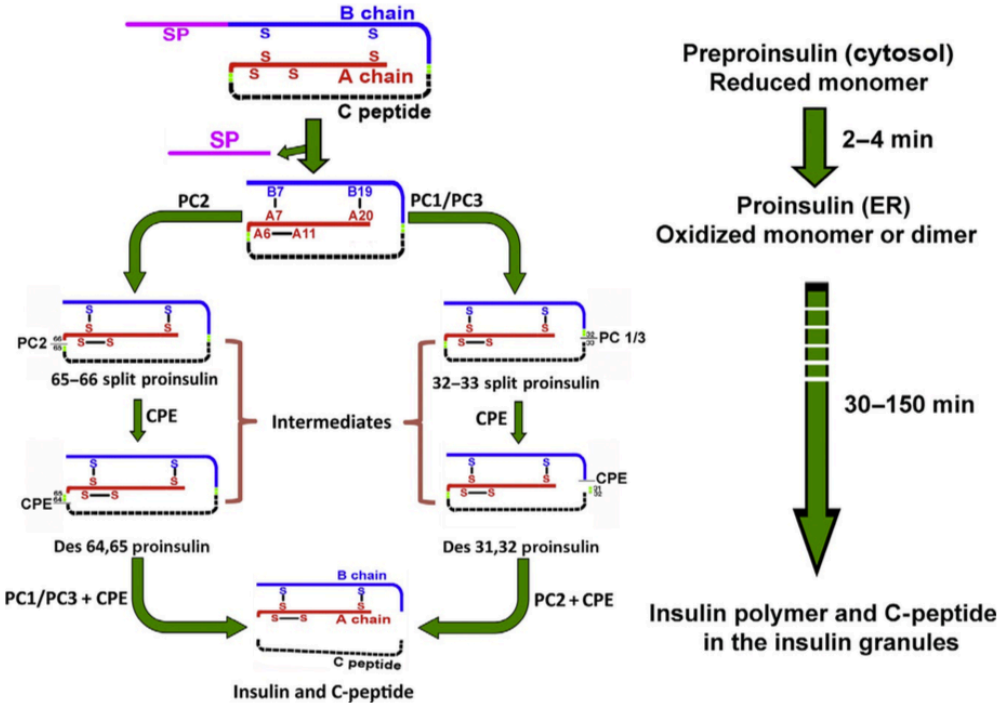


Figure 3 Insulin biosynthesis (1)
SP = signal peptide, blue = β-chain, red = α-chain, black = C-peptide, ER = endoplasmic reticulum, PC = proprotein convertase, CPE = carboxypeptidase

During extra uterine life the amount of secreted insulin is determined by the amount of blood glucose. Sugar is carried into the β-cell by a transporter called GLUT2. Within the cell the molecule gets oxidized and ATP is generated. As a consequence of this ATP-dependent potassium channels close and the β-cell membrane gets depolarized, which leads to an opening of calcium channels. Extracellular calcium enters the cell and activates exocytosis of insulin (Figure 4) (2).

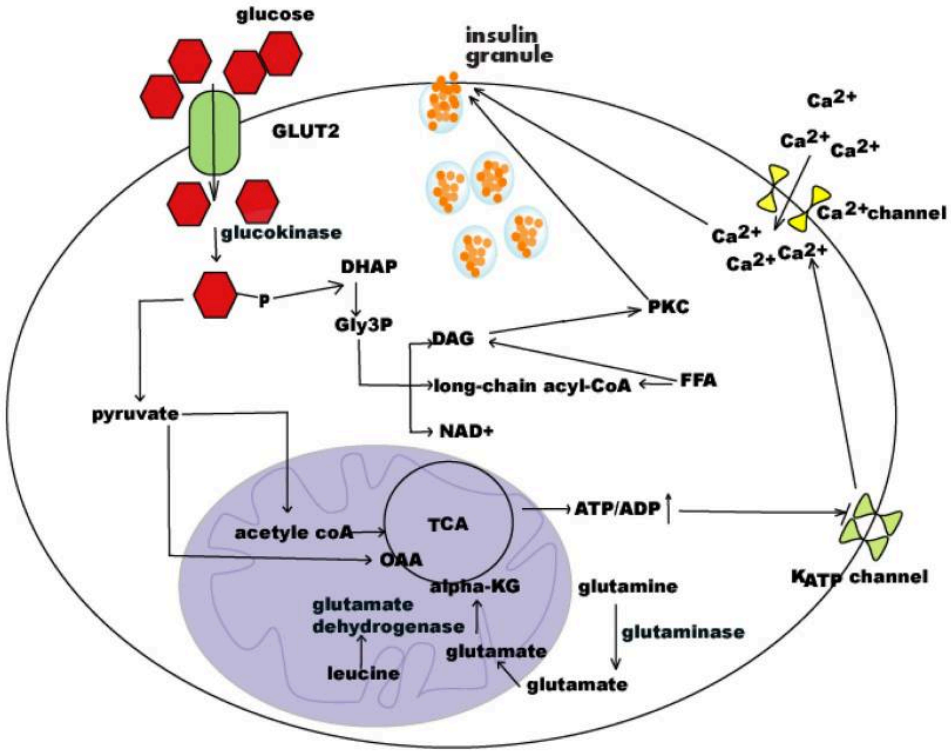


Figure 4 Glucose stimulated insulin secretion (2)
GLUT2 = glucose transporter type 2, DHAP = dihydroxacetonphosphate, Gly3P = glycerol 3-phosphate, DAG = diacylglycerol, CoA = coenzyme A, NAD+ = nicotinamidadeninnucleotide, PKC = proteinkinase C, FFA = free fatty acid, Ca^{2+} = calcium, K = potassium, TCA = tricarboxylic acid, OAA = oxaloacetate, alpha-KG = alpha ketoglutaric acid, ADP = adenosine di-phosphate, ATP = adenosine tri-phosphate

After neonatal adaption to the extra-uterine environment, insulin and glucagon become responsible for maintaining normoglycemia and glucose becomes the main stimulus for the pancreatic hormone secretion. The higher the glucose concentration in the blood the more insulin is secreted from pancreatic β-cells to maintain normoglycemia (26).

Furthermore the pancreatic activity depends on inhibiting sympathetic and stimulating parasympathetic influences. The autonomic nervous system connects the brain, which sets boundaries for the aimed amount of blood glucose, to the pancreas. A_2-adrenoceptors can cause an opening of potassium channels and a subsequent inhibition of insulin secretion. On the other hand muscarinic cholinoceptors can deactivate potassium channels and push the cell to secrete insulin (29).

1.4 The Effect of Maternal Diabetes on the Fetus

For a better understanding of one of the most important risk factors for neonatal hyperinsulinema, maternal diabetes, it is necessary to explain the pathomechanism in relation to the fetus.

According to the Pedersen hypothesis (10), especially in poorly controlled diabetes, the mother shows phases of transient or even chronic hyperglycemia. As glucose can, in comparison to insulin, which cannot, cross the placenta, the fetus is also hyperglycemic. As mentioned above during its intra-uterine life the neonate does not produce insulin to maintain stable blood glucose. But a chronic fetal hyperglycemia somehow stimulates the pancreatic β-cells and constantly more insulin is produced (18). Studies performed in sheep showed that chronic constant maternal hyperglycemia leads to an increased apoptosis of fetal pancreatic β-cells, even though size and degree of cell mitosis remained unaffected. Due to the apoptosis, the pancreas produced initially less insulin. Furthermore, chronic pulsatile hyperglycemia leads to an increase of β-cells but not to an increase of insulin production, suggesting a dysfunction of fetal pancreatic β-cells in sheep (30). As those results are contradictory to the majority of studies presented in this thesis, showing that chronic maternal hyperglycemia, as seen in diabetes, does lead to fetal hyperglycemia, it can be assumed that exact mechanisms of maternal hyperglycemia on the fetal pancreas are not fully understood so far.

At the time of birth when the umbilical cord is cut, the fetus suddenly looses its connection to the mother and also the glucose supply ceases. But as the newborns' pancreas is used to producing a lot of insulin, way more than needed under these new metabolic conditions is produced and dangerous neonatal hypoglycemia with possible subsequent neurological damage occurs. The newborn needs up to hours to adjust to these new circumstances and has to be treated with oral or intravenous glucose until then to maintain normoglycemia (26).

As insulin also acts as a growth factor during the fetal life *in utero*, hyperinsulinemic newborns tend to have more body fat and, hence, to be heavier. The heavier and bigger the newborn is the higher the risk of birth complications like shoulder dystocia, fetal or maternal injuries and ceasing of contractions and a subsequent caesarean section (15).

1.4.1 Effects on the Later Life of the Child

As first proposed by D.J.P. Barker, not only genes are responsible for human development, but also environmental factors (31-34). The so called thrifty phenotype hypothesis suggests that if the fetal nutrition *in utero* is compromised, the child is more prone to developing cardiac and metabolic diseases, especially type 2 diabetes, later in life. The reason for this risk is an impaired growth of fetal pancreatic β-cells due to malnutrition.

Keeping this hypothesis in mind it seems logic that fetal over-nutrition and over-supplementation with glucose can also cause metabolic disturbances later in life. A high protein and high fat diet during pregnancy can increase the child's risk of developing type 2 diabetes later in life, as well as maternal alcohol intake (35-37). But probably the biggest risk factors for an impaired glucose tolerance later in life is maternal obesity and maternal insulin resistance and an elevated gestational glucose concentration with subsequent fetal hyperglycemia *in utero* (38-40).

This over-nutrition seems to cause a neuro-endocrine malprogramming of metabolic processes leading to obesity, diabetes and cardiovascular diseases of the child later in life (Figure 5) (41-44).

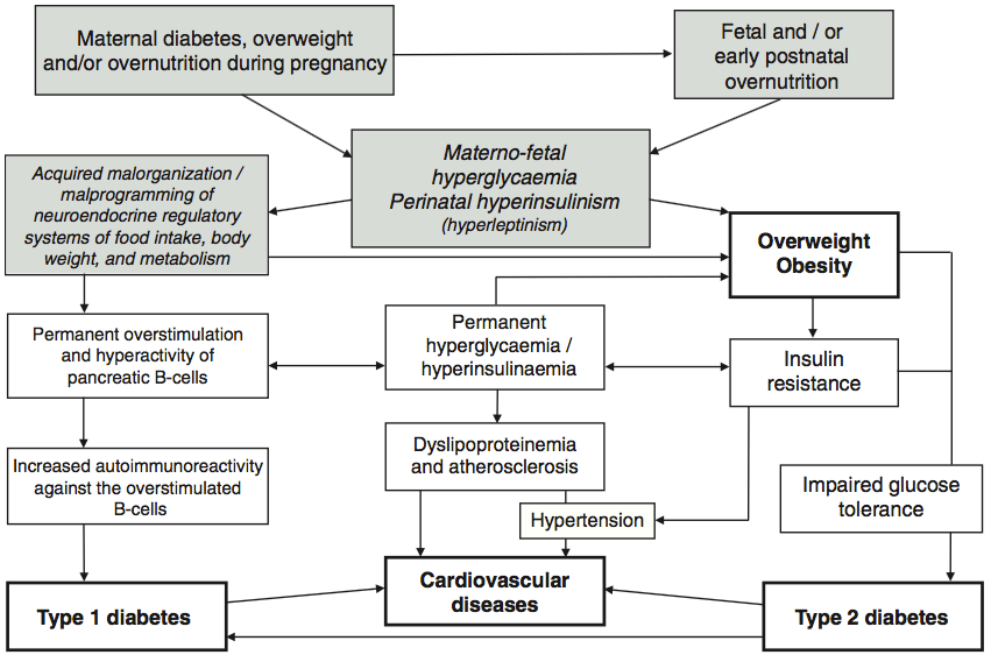


Figure 5 A model of possible developmental diabetogenic pathways pre- and postnatal (45)

2 Methods

As this thesis is a narrative review of knowledge gained by others, the literature research was performed using public databases.

2.1 Hypothesis

Following hypothesis should be testet in this thesis: What modifies the neonatal insulin level straight after birth?

To do this, following steps were taken:

1. Summarizing current knowledge regarding causes of neonatal hyperinsulinism.
2. Dividing causes into perinatal, parental, external and fetal and neonatal.
3. Going into detail about different influences within those topics.
4. It is not the goal to describe the consequences of altered fetal and neonatal insulin levels on the later life of the newborn.

2.2 Search Strategy

1. Primary literature search on PubMed, PMC and Google Scholar.
2. Keywords used for the search are: insulin, fetus, neonate, cord blood, umbilical cord, C-peptide and proinsulin. The search was refined with more specific keywords depending on the subtopic.

Section	Keywords
Perinatal Modifiers of Insulin in the Newborn	fetal sex, male, female, boy, girl, gender, vaginal delivery, caesarean section, instrumental delivery, ethnicity, European, Asian, African, American, twin, gestational age, large for gestational age, small for gestational age, neonatal size

Parental Influences	maternal glucose intolerance, maternal diabetes, diabetes mellitus, gestational diabetes, DM1, DM2, maternal obesity, maternal body weight, maternal BMI, maternal smoking, maternal lifestyle, maternal diet, maternal HIV, paternal insulin resistance, paternal diabetes, paternal disease
External influences	oral anti-diabetics, diabetic treatment, maternal medication, glucocorticoids, cortisol, glucose infusion, tocolysis, indomethacin, prostaglandin, altitude
Fetal and Neonatal Diseases	erythroblastosis, fetal disease, IRDS, nesidoblastosis, hereditary hyperinsulinemia, leprechaunism, Donohue syndrome, hyperammonemia, Beckwith-Wiedemann syndrome, Sotos syndrome, Kabuki syndrome, Russell-Silver syndrome

Table 2 Section specific keywords

3. There were no limitations to the year of publication but only articles with abstracts in German and English language are included.
4. Evaluation of relevance of the literature due to the title and the abstract.
5. Secondary search using source lists of relevant articles to find more relevant literature.
6. The literatures publishing dates reach from 1952 until July 2018.

Articles are relevant if the content is at least partly about neonatal insulin concentrations measured in the umbilical vein or artery. Blood samples not taken from the neonatal umbilical cord but from peripheral veins or capillaries are considered in cases lacking of data from the umbilical cord and, if so, are further described.

Also articles covering umbilical cord C-peptide, proinsulin and 32-33 split proinsulin were included in this analysis.

Data were not excluded due to the use of different methods of laboratory hormone measurement (ELISA, RIA etc.) or study methods (retrospective, prospective etc.).

Due to data being indicated in different units, units of insulin and C-peptide have been converted to the SI-units pmol/l for insulin and nmol/l for C-peptide (46, 47). The used conversion factor for µU/mL insulin to pmol/l insulin is 6.945 (1 µU/ml = 6.945 pmol/l). The used conversion factor for ng/ml C-peptide to nmol/l C-peptide is 0.3 (1 ng/ml = 0.3 nmol/l) and 0.001 for pmol/l C-peptide to nmol/l C-peptide (1 pmol/l = 0.001 nmol/l) (48). Exceptions of converting the hormone concentrations into SI-units are made in Figure 9, Figure 10, Figure 12 and Figure 14 due to better illustration.

Only articles dealing with association with altered fetal or neonatal insulin levels were considered. Papers reporting about effects of fetal or neonatal hypo- or hyperinsulinism on the fetus and its later development were excluded.

2.2.1 Inclusion criteria

- Fetal cord blood values of at least one of the following hormones: insulin, C-peptide, proinsulin or 32-33 split proinsulin.
- Studies comparing a control population with a population influenced either by non-pathological, external, parental or fetal/ neonatal factors, which are possibly altering the neonatal insulin level after birth.

2.2.2 Exclusion criteria

- Studies covering only insulin-like-growth-factors 1 and 2 and not insulin itself.
- Any kind of animal like “rat” or “primate” and the term “non-human” itself.
- Measurements of hormones in blood not drawn straight after birth.
- Articles dealing with the consequences of fetal hypo- or hyperinsulinism and its impact on later life.

2.3 Limitations

Relevant articles not listed on PubMed, PMC or Google Scholar can only be found by coincidence. Furthermore articles dealing with fetal hypo- or hyperinsulinism only marginally could be overlooked because of a missing description in the title or abstract.

Also articles written in languages other than German or English cannot be included due to a lack of understanding.

Because of the limited number of study participants in some publications, it is questionable if the outcomes are always reproducible and significant.

3 Results

3.1 Perinatal Modifiers of Insulin in the Newborn

3.1.1 Fetal Sex

Female neonates have raised proinsulin (8, 9, 49) and 32-33 split proinsulin (8, 9, 49, 50) levels in their cord blood compared to males (Figure 6).

There are disparities concerning published results of insulin and C-peptide levels. Some studies report that there is no sex difference in insulin (8, 9, 49, 51) and C-Peptide (8, 49) concentrations, but there are also papers that report a difference in insulin (50, 52-54) and C-Peptide (52, 55) levels of male and female newborns. The overall tendency is upon no sex difference in insulin and C-peptide concentrations as studies showing this result have larger numbers of participants.

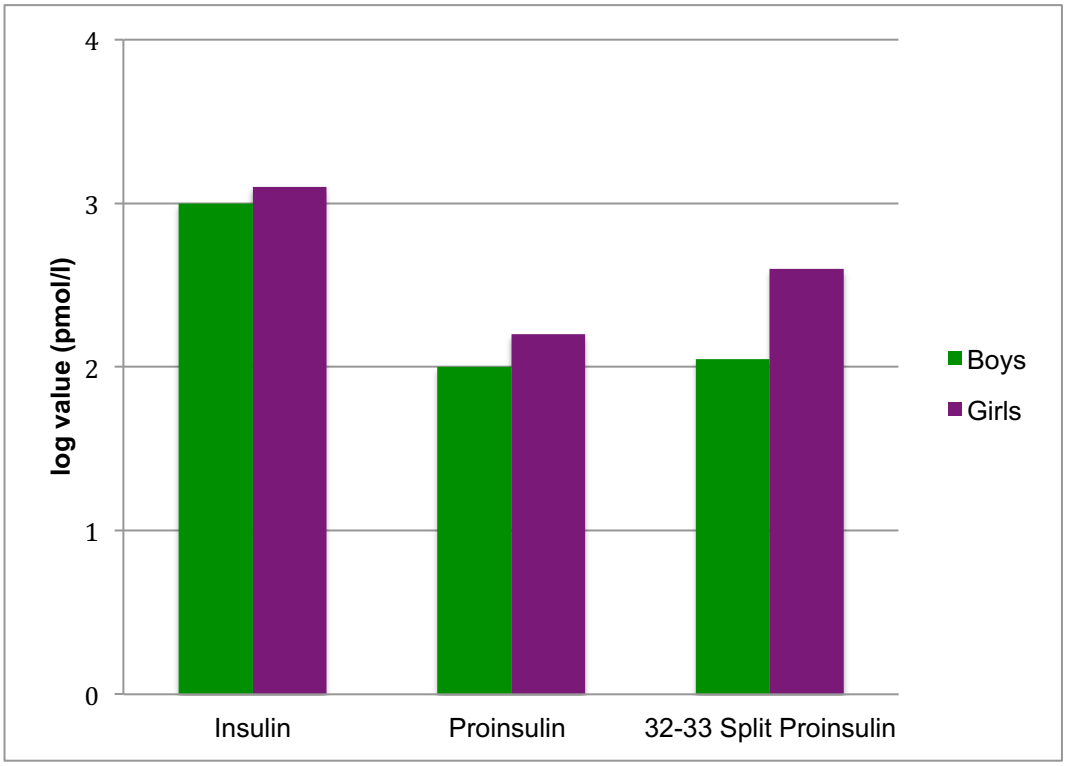


Figure 6 Influence of gender on insulin, proinsulin and 32–33 split proinsulin (9)
p-value < 0.05 for effect of gender for proinsulin and 32-33 split proinsulin, n= 21 male/ 28 female (figure 3 of the original publication was converted into data shown here and may not necessarily reflect the exact values of the original study)

Also the difference in cord proinsulin and 32-33 split proinsulin concentration between boys and girls, girls having higher values, remains significant in offspring of type 1 diabetic mothers (9), whereas other authors report that umbilical cord C-peptide concentrations in boys are much more influenced by gestational diabetes than in female offspring (56).

3.1.2 Mode of Delivery

Newborns delivered via Caesarian section have higher values of cord insulin (8, 50, 57, 58) and C-peptide (8) than newborns delivered vaginally.

There is also a difference within the settings of a vaginal delivery. Ventouse extraction or use of forceps leads to higher insulin concentrations than seen after a normal vaginal delivery (Figure 7) (8, 58).

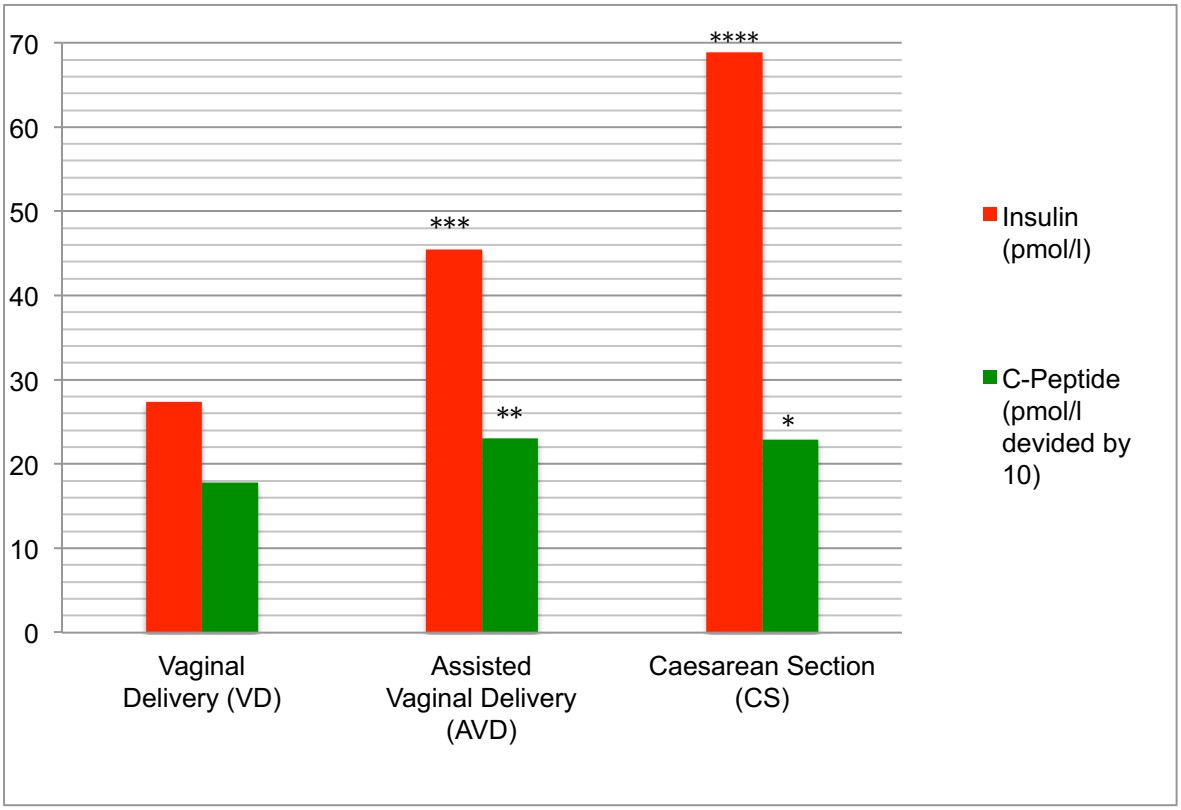


Figure 7 Insulin and C-peptide concentrations by mode of delivery (8)
C-Peptide values in the figure are multiplied by 100 for better visibility. True mean values: Insulin (pmol/l) = 27.4 (VD), 45.5 (AVG), 68.9 (CS); C-peptide (nmol/l) = 0.177 (VD), 0.230 (AVD), 0.229 (CS); p-values: * = 0.1, ** = ≤0.05, * = ≤0.001, **** = ≤0.0001; n = 391/ 291 (C-peptide), SD not given in the original publication**

This is not a uniform finding. There are also reports of insulin concentrations being lower in newborns delivered with instrumental assistance than those of infants born via normal vaginal delivery: 41.7 vs. 39.2 pmol/l ($P < 0.001$, no SD given) (50).

Some studies also report that there is a difference in insulin concentrations within modes of Caesarian section. The amount of insulin in the newborns' cord blood is higher if there was a primary spontaneous onset of labor, which later arrested and led to an emergency Caesarean section than in scheduled interventions without complications (Table 3) (50, 54, 55).

	Cord Insulin (pmol/l)		
Mode of Delivery	Mean (s.e.)	95% CI	n
Normal Spontaneous Delivery	50.7 (2.8)	45.1-56.3	147
Caesarean without Labor	72.2 (6.3)	59.7-84.7	112
Caesarean due to Arrest of Labor	53.5 (6.3)	50.0-66.0	16

Table 3 Insulin levels depending on the mode of delivery (57)
$p < 0.001$, s.e. = standard error, CI = confidence interval

Interestingly, the mode of delivery also influences pancreatic hormone levels in neonates of diabetic mothers. The cord blood insulin of their newborns is higher when born via elective caesarean section than when born vaginally or by emergency C-section. This dependency could be masked by the fact that women suffering from diabetes deliver more often via Caesarean section. But as insulin levels in neonates of diabetic mothers are higher in operative deliveries but levels of proinsulin and 32-33 split proinsulin are not, it can be hypothesized that the mode of delivery is an independent factor altering cord insulin levels (9).

3.1.3 Twin Pregnancy

There are twin studies showing that the heavier twin has higher cord blood insulin than the smaller or intrauterine growth restricted (IUGR) twin (59). Interestingly, there is a difference between weight-concordant and discordant monozygotic twins. Discordancy in this study is defined as a weight difference bigger than 20%. Outcomes concerning weight within the twin pairs are the same as in previously mentioned studies, but the discordant twin pair showed higher levels of cord insulin than the concordant pair (Table 4) (60).

	Larger twin			Smaller twin		
	Discordant	Concordant	p	Discordant	Concordant	p
Insulin	149.3	46.5	< 0.02	101.4	34.7	< 0.03
SE	5.3	1.8		2.9	2.3	

Table 4 Cord insulin concentrations in the larger and smaller twin divided by discordancy (60)
Values given are mean, SE = standard error, n= 20 (discordant)/ 20 (concordant), insulin in pmo/l

3.1.4 Gestational Age

Not only the size and weight at birth seem to be associated with the neonatal cord blood insulin concentration but also the gestational age at which the child is born.

Very preterm infants (≤ 30 weeks) show markedly raised cord insulin, 0., proinsulin and 32-33 split proinsulin concentrations at birth compared to late preterm (35-37 weeks) and full term (≥ 38 weeks) neonates (Figure 8) (6, 54, 61-64). There also is a decline in insulin concentrations with increasing gestational age within 37-42 weeks (51).

Neonates suffering from intrauterine growth restriction (IUGR) show lower cord insulin levels than their normal sized counterparts (59, 65-67).

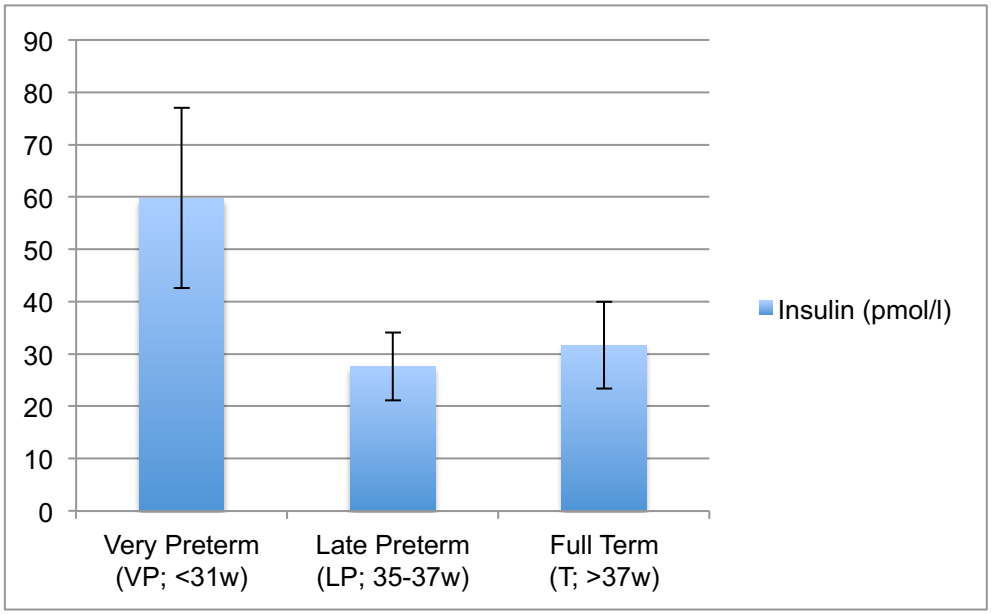


Figure 8 Cord blood insulin concentration depending on the gestational age at birth (6)
p < 0.001 for VP, other p-values not given, n = 16 (VP)/ 18 (LP)/ 18 (T)

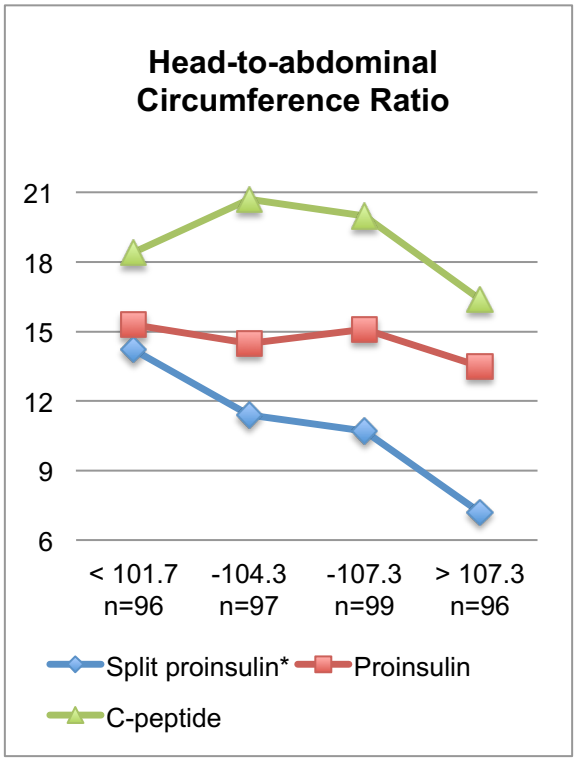
3.1.5 Neonatal Anthropometric Parameters at Birth

Cord insulin and C-peptide are lower in the short for gestational age (SGA, < 10th centile) group compared to the average and large infants (51, 68-71) (Table 5) and also differ between average for gestational age (AGA) and large for gestational age (LGA, > 90th centile) infants, which have higher C-peptide cord blood concentrations (72, 73). The same dependency of insulin, C-peptide, proinsulin and 32-33 split proinsulin is also seen with increasing birth weight (63, 74) and macrosomia (birth weight > 4000g) (75, 76).

	LGA	AGA	SGA
C-peptide (nmol/l)	0.333 ± 0.2 (0.133 – 0.932)	0.333 ± 0.2 (0.133 – 0.666)	0.2 ± 0.133 (0.133 – 0.333)
Insulin (pmol/l)	52.8 ± 44.4 (13.9 – 172.2)	45.1 ± 44.4 (15.3 – 147.2)	27.1 ± 32.6 (4.2 – 123.6)
n	15	15	15

Table 5 Insulin and C-peptide in the cord blood of LGA, AGA and SGA infants (68).
Values are mean ± standard deviation (range), p < 0.05 compared with the other two groups

Hormone levels not only depend on weight, but also on body proportions (77, 78). The higher the ponderal index is, the higher the cord blood insulin (51), proinsulin and 32-33 split proinsulin concentrations are (Figure 10). The lower the head to abdominal circumference ratio the higher the split proinsulin (Figure 9) (8).



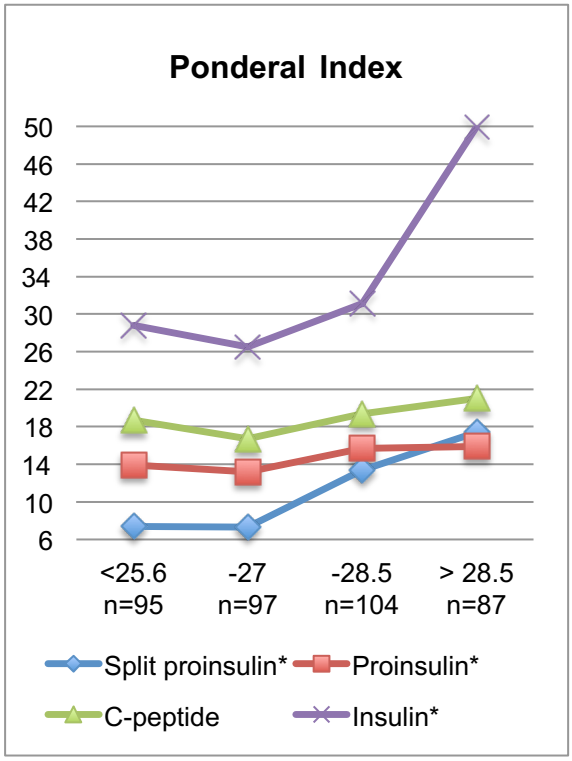


Figure 9 Cord blood concentrations of split proinsulin (pmol/l), proinsulin (pmol/l) and C-peptide (pmol/dl) according to the infants head-to-abdominal circumference ratio (8)
p-value: <0.0001 (split proinsulin), 0.06 (proinsulin), 0.8 (C-peptide), p-values indicate the significance of the associations of different pancreatic hormones with the head-to-abdominal circumference ratio, * = significant

Figure 10 Cord blood concentrations of split proinsulin (pmol/l), proinsulin (pmol/l), C-peptide (pmol/dl) and insulin (pmol/l) according to the infants ponderal index (8)
p-value: <0.0001 (split proinsulin), 0.0004 (proinsulin), 0.2 (C-peptide), 0.004 (insulin), p-values indicate the significance of the associations of different pancreatic hormones with the ponderal index, * = significant

3.2 Parental Influences

3.2.1 Maternal Glucose Intolerance and Diabetes

If the maternal glucose axis does not work properly, it also affects neonatal insulin levels. It is well known that maternal diabetes is one of the biggest risk factors for elevated insulin levels in the neonate and potentially life threatening hypoglycemia.

Even pre-diabetic, mild gestational glucose intolerance leads to a raised concentration of insulin (79), proinsulin (80) and C-peptide (81, 82) in the cord blood (Figure 11).

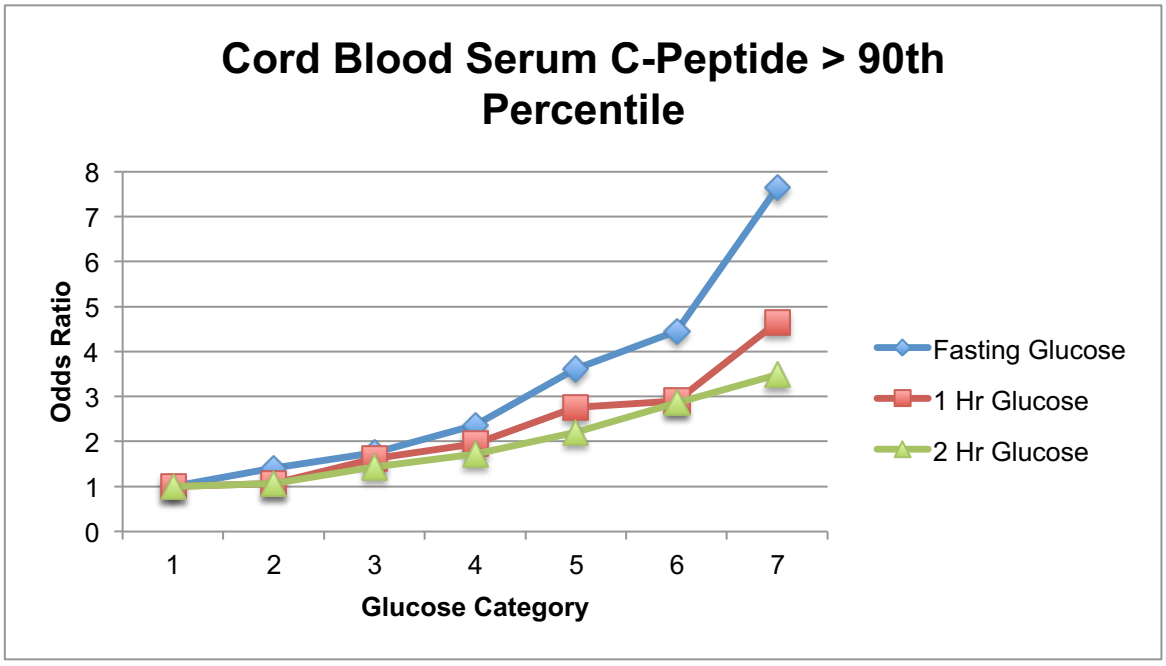


Figure 11 Odds ratio for having a cord insulin concentration > 90th percentile while the mother being in a specific glucose category at different times of an OGTT performed between 24 and 32 weeks of gestation (81)
Glucose categories: fasting plasma glucose level — category 1 = <75 mg/dl, category 2 = 75 - 79 mg/dl, category 3 = 80 - 84 mg/dl, category 4 = 85 - 89 mg/dl, category 5 = 90 - 94 mg/dl, category 6 = 95 - 99 mg/dl, category 7 = >99 mg/dl; 1-hour plasma glucose level — category 1 = <106 mg/dl, category 2 = 106 - 132 mg/dl, category 3 = 133 - 155 mg/dl, category 4 =156 - 171 mg/dl, category 5 = 172 - 193 mg/dl, category 6 = 194 - 211 mg/dl, category 7 = >2111 mg/dl; 2-hr plasma glucose level — category 1 = <91 mg/dl, category 2 = 91 - 108 mg/dl, category 3 = 109 - 125 mg/dl, category 4 = 126 - 139 mg/dl, category 5 = 140 - 157 mg/dl, category 6 = 158 - 177 mg/dl, category 7= >177 mg/dl
n: 19885 (C-peptide measured)/ 1671 (C-peptide > 90th centile), p-values not given in the original publication

3.2.1.1 Gestational Diabetes (GDM)

Gestational Diabetes is associated with elevated levels of cord blood insulin (83), proinsulin (80), 32-33 split proinsulin and C-peptide (82, 84-89) in the neonate compared to offspring of healthy mothers.

The severity of GDM, assessed by an OGTT performed after birth, also seems to play a role in fetal hormone concentrations (Table 6) (85).

	Normal OGTT	IGT/IGF	DM2
Insulin	57 (40 – 94)	83 (31 – 162)	101 (61 – 198)
n	50	20	32
Proinsulin	13 (9 – 15)	12 (10 – 16)	19 (14 – 24)
n	48	21	34
32-33 s. proi.	21 (12 – 42)	31 (8 – 50)	42 (25 – 78)
n	48	21	34

Table 6 Neonatal outcome by maternal diabetic state after pregnancy in women suffering from GDM during pregnancy (85)
Data are means; data in parenthesis are interquartile ranges, s. proi. = split proinsulin, all values given in pmol/l, OGTT = oral glucose tolerance test, IGT = impaired glucose tolerance, IGF = impaired fasting glucose, DM2 = type 2 diabetes mellitus, P < 0,05, OGTT performed during pregnancy (not further specified in original publication) and at 8 weeks after birth

3.2.1.2 GDM and Obesity

Even higher values of cord hormone parameters are seen if GDM is combined with maternal obesity. In GDM alone 16% (2.9 OR, n = 2419) of infants show a cord C-peptide > 90th centile and only 11% (1.8 OR, n = 1829) of the offspring of obese mothers without GDM whereas 22.4% (4.14 OR, n = 751) of infants of obese mothers suffering from GDM have an elevated cord C-peptide > 90th centile (90).

3.2.1.3 Diabetes Mellitus Type 1 and 2

Insulin, proinsulin, 32-33 split proinsulin and C-peptide are also higher in newborns of mothers that have been diagnosed with overt diabetes, either type 1 (9), type 2 (85, 91) or maternal pre-pregnancy diabetes not further specified (84, 87, 92-95).

The difference of fetal insulin secretion, influenced by different maternal diabetic states (healthy, pre-gestational DM, GDM), is also already measurable in the amniotic fluid (Table 7) (87, 96).

		Insulin (pmol/l)	
Groups	N	Mean	SEM
GDM1	18	231.3	69.5
GDM2	15	133.3	29.9
IDDM	11	147.2	33.3
NM	37	51.4	6.9

Table 7 Insulin values in amniotic fluid taken at 36-40 weeks gestational age (87)
GDM1 = gestational diabetes mellitus treated with diet, GDM2 = treated with insulin, IDDM = insulin dependent diabetes mellitus (not further specified in original publication), NM = non-diabetic mothers, SEM = standard error of mean

3.2.1.4 Gestational Diabetes compared to Pre-pregnancy Diabetes

There is no consensus about insulin, C-peptide, proinsulin and 32-33 split proinsulin being higher in GDM or in pre-gestational diabetes type 1 or 2, some stating hormone concentrations are higher in offspring of mothers suffering from gestational diabetes (88) and some stating it is higher in neonates of pre-gestational diabetic mothers (84, 85, 93, 97).

Studies that concluded higher hormone levels in offspring of pre-gestational diabetic mothers had higher numbers of participants. Results of the biggest study are presented in Table 8.

	Control	GDM	Type 2 Diabetes
Cord Insulin (pmol/l) n	33 (18 - 62) 92	67 (42 - 135) 133	77 (42 - 143) 36
Proinsulin (pmol/l) n	10 (8 - 13) 93	14 (10 - 19) 134	16 (10 - 26) 38
32-33 split proinsulin (pmol/l) n	7.6 (5.6 – 15.6) 93	27 (10 - 52) 134	26 (13 - 70)* 38

Table 8 Cord insulin depending on type of diabetes (85)
Data in means, data in parenthesis showing the interquartile range, p < 0.05 vs. control, * = p > 0.05 vs. control

3.2.2 Diabetic Control

Not only the type of Diabetes contributes to the neonatal insulin outcome but also if and how the condition is managed.

A poor maternal metabolic control, measured by the degree of maternal glycosuria, hypoglycemia and ketonuria, leads to increased levels of neonatal cord blood C-peptide concentrations (98).

Newborns of mothers treated with diet alone show lower values of insulin concentrations in their cord blood than offspring of insulin treated mothers (Table 9) (99). But the condition of the women treated with diet or metformin was not as severe (White class A) as the condition of the patients treated with insulin (White class B-F). This is not a uniform finding (87, 97).

		Insulin (pmol/l)		
White Class	n	25	50	75
A	9	27.8	55.6	72.9
B - F	18	296.6	805.6	1368.3

Table 9 Cord vein insulin in newborns of White Class A and B-F diabetic mothers (99)
25/ 75 = 25th/ 75th percentile values of insulin, 50 = median; p < 0.001; White Class A = mothers treated with diet and/or metformin, White Class B-F = mothers treated with insulin

3.2.3 Maternal Obesity

The maternal BMI plays a very important role in pregnancy outcomes. Offspring of mothers with an elevated BMI show significantly elevated cord blood insulin (80, 100-102) and C-peptide (3, 62, 90, 103-105) concentrations in comparison to children of non-obese mothers.

Not only the BMI during pregnancy influences the fetal outcome. There is also a positive correlation of cord blood insulin and C-peptide with pre-pregnancy BMI (101) and gestational weight gain (62, 77, 100, 103, 106).

In addition to that the more overweight a woman is the more insulin resistant she gets. That is also affecting the fetus, which shows higher values of cord C-peptide, if the mother is obese. But the mother does not even have to be within the BMI range for obesity to affect the fetuses' insulin production. The higher the maternal BMI, even within the non-pathological range, the more insulin and C-peptide is produced by the newborn (Figure 12) (3).

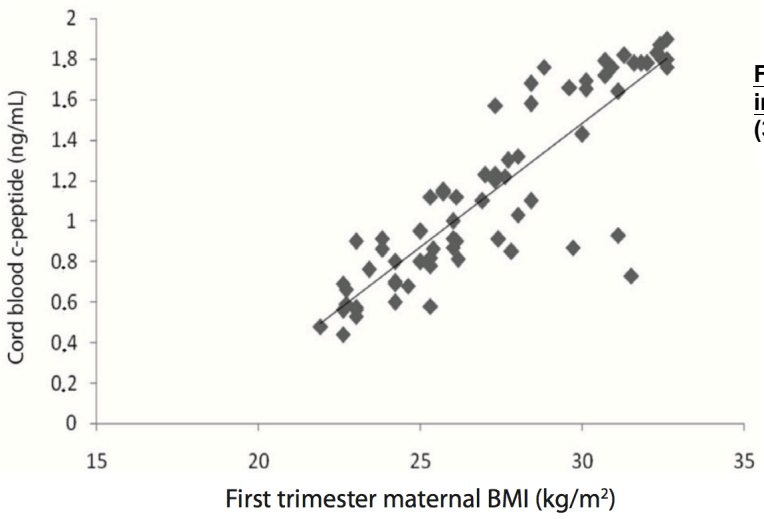


Figure 12 Neonatal cord C-peptide in dependency on the maternal BMI (3) p = 0.035, r = 0.74

3.2.4 Maternal Infection

Maternal urinary tract infection has an altering effect on neonatal insulin level measured in the umbilical vein. Depending on the severity of the infection, classified by the maternal procalcitonin (PCT) level, neonates show different degrees of hypoinsulinemia (Table 10) (107).

		PCT in Mother (ng/l)		Neonatal Cord Insulin (pmol/l)	
Group	n	Mean	SD	Mean	SD
Control	12	0.5	0.0	50.7	12.5
Group 1	15	1.2	0.5	29.2	4.9
Group 2	12	3.9	0.7	12.5	7.6
Group 3	9	7.3	1.8	13.9	8.3

Table 10 Serum insulin of neonates born to mothers with urinary tract infection (107).
n = number, SD = standard deviation; p ≤ 0.05

3.2.5 Maternal Lifestyle

There is little research about how maternal diet influences the insulin level of the neonate, but there is evidence that some nutritional components lower the fetal insulin and, as a result of this, elevate the glucose level of the newborn and help preventing hypoglycemia (49, 108, 109).

A **high-carbohydrate diet** (>75% of total intake is caloric) within 24h before labor increases the risk for neonatal hypoglycemia 11-fold independent of the maternal diabetic state.

Another factor that has to be taken into account is **maternal physical activity**. The risk of neonatal hypoglycemia is five times higher if the mother does not conduct more than 40 minutes of at least moderate physical activity, like walking or housework, within 24h before delivery (110).

For further explanation of the data about high-carbohydrate intake and maternal physical activity see section 4.3.

Maternal smoking also affects the neonatal insulin concentration in the cord blood. Infants of mothers, who smoked before and during pregnancy, show lower cord blood insulin levels than offspring of non-smoking women (111, 112) but those results are contradictory to other studies, showing that the neonates of

mothers, who smoked during pregnancy or were former smokers have slightly higher cord blood insulin levels than offspring of non-smoking mothers (p-values not given) (113).

3.2.6 Paternal insulin resistance

There are many studies demonstrating that maternal insulin resistance or diabetes has a significant effect on neonatal insulin concentrations but the fathers' metabolic state is also associated with altered neonatal insulin concentrations in the cord blood. Paternal insulin resistance has a negative effect on neonatal insulinemia. The more resistant the father is, the higher the insulin concentration in the cord blood of his offspring is. Those values increase even more if there is an additional insulin resistance on the mothers' side (Figure 13) (7).

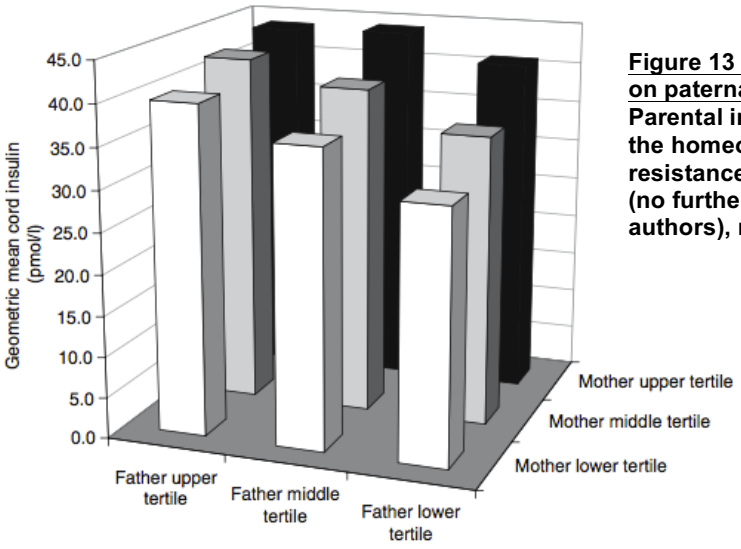


Figure 13 The fetal cord insulin in dependency on paternal and maternal insulin resistance (7) Parental insulin resistance was calculated with the homeostasis model assessment of insulin resistance (HOMA-IR) and divided into tertiles (no further information provided by the authors), n =644

3.2.7 Ethnicity

Indians show higher *post partum* insulin concentration in comparison to **Caucasian** newborns: 55.5 (34.7 – 104.9) vs. 13.9 (13.9 – 34.7) pmol/liter (p = 0.002, n = 50/25) (114), but this is not a uniform finding (115).

The same authors also reported that **Polynesian** neonates show higher cord insulin levels compared to **Europeans** and **South East Asian** newborns (Table 11) (115, 116).

North African newborns also showed higher C-peptide concentrations than **Belgian** newborns: 0.125 vs. 0.110 nmol/l (p = 0.04, n = 184/89, SD not given) (117).

	Europeans	South East Asians	Polynesians
Cord Insulin (pmol/l)	86.1	77.8	91.7

Table 11 Geometric mean of neonatal cord insulin concentrations stratified by ethnicity (116)
p < 0.001, n = 26 (E)/ 11 (SEA)/ 55 (P), SD not given in original publication

3.3 External Influences

3.3.1 Pharmacology

3.3.1.1 Glucose

Many drugs used for various reasons during labor and delivery, for example oxytocin, are given via a glucose containing infusion, which affects the fetal insulin metabolism.

Cord insulin levels depend on the duration of glucose application. The longer it is infused the higher the neonatal insulin concentration gets (Figure 14) (5, 118).

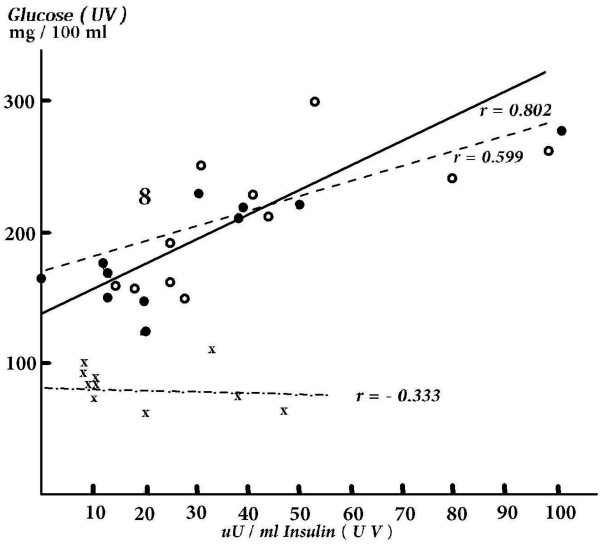


Figure 14 Correlation between glucose and insulin levels in venous cord blood during the infusion of glucose and glucose with insulin (5) Infusions given during the 2nd stage of labor, UV = umbilical vein, 10% glucose/1g per min = -•-•- (n = 12), 10% glucose/1g per min + 1U crystalline insulin per 3g glucose/0.33U per min = -o-o- (n = 13), control = -x-x- (n = 11)

It is also relevant how many hours *ante partum* the glucose is given. Neonatal levels of insulin are higher if the glucose infusion (5%) is given 1h *ante partum* than if given 2.5h *ante partum* (119). If there is too little time between glucose administration and delivery, neonatal cord blood insulin concentrations sink again. After a single 25g glucose injection into the maternal vein the neonatal insulin levels are higher if the mother received glucose 61-100 minutes prior delivery than if she received it only 4-20 minutes before. That is due to the duration of the insulin response to glucose in the fetus (120).

3.3.1.2 Oral Anti-diabetic Treatment (OAD)

There is a lack of information about how fetal secretion of cord insulin, C-peptide, proinsulin and 32-33 split proinsulin react to a maternal diabetes treatment with OADs. There are a few studies on metformin and glyburide stating that there is no difference between hormone concentrations in newborns of mothers treated with OADs and mothers treated with placebo (121) or insulin (122, 123).

For further information about the influence of a diabetic treatment with insulin see section 3.2.2.

3.3.1.3 Oral Glucocorticoids

Oral glucocorticoids given to the mother is a standard treatment to reduce neonatal complications in premature born infants.

A study conducted with more mature infants (> 35w GA) born via caesarean section showed that a single 12mg dose of betamethasone given to the mother approximately 24h before birth leads to a significant increase in neonatal cord C-peptide. Values in treated newborns were more than double of that in untreated ones (124).

Interestingly, newborns with a cushingoid appearance also show elevated cord insulin levels (63).

3.3.1.4 Tocolytic Therapy

Newborns of women receiving a tocolytic treatment with fenoterol, terbutalin, ritodrine or isoxsuprine show elevated cord insulin levels (125, 126) or suffer from hypoglycemia within hours after birth (127).

3.3.1.5 Antiretroviral Therapy

Newborns of mothers suffering from the human immunodeficiency virus (HIV) show different levels of cord insulin depending on the type of treatment the women receives. Neonates of mothers treated with zidovudine show lower cord insulin levels than newborns of the control group and the insulin values of neonates born to women treated with the triple therapy (zidovudine, lamivudine and nelfinavir) are lowest (Table 12) (128).

		Cord insulin (pmol/l)	
Group	n	Median (range)	p
Control	12	45.1 (20.8 – 66.0)	-
Zidovudine	18	33.3 (5.6 – 62.5)	0.35
Triple therapy	22	20.1 (12.5 – 33.3)	0.047

Table 12 Different HIV treatments altering neonatal insulin levels (128).
n = number, triple therapy = zidovudine, lamivudine and nelfinavir

3.3.2 Environment

Dialkylphosphate metabolites of various organophasphate insecticides, which can be measured in the mothers' urine, cause a non-linear increase in neonatal cord insulin (129).

Also **particulate air pollutants**, especially $PM_{2,5}$, cause a rise in cord insulin. $PM_{2,5}$ stands for particulate matter with 50% of particles being 2.5 µm in diameter and > 25% smaller particles and < 25% larger particles than 2.5 µm in diameter. If there is an additional load of 2.4 $\mu g/m^3$ of $PM_{2,5}$ during pregnancy, there is an increase of 15,8% of neonatal cord blood insulin level at birth which is comparable with an increase of the early pregnancy BMI by 9 kg/m^2 (130).

Furthermore, residence at **high altitude** has an impact on the neonatal insulin levels. Newborns of mothers living at an altitude of 3600m above sea level showed lower umbilical cord insulin levels (median = 53.5 pmol/l; $p < 0.01$) than neonates born to mother living 400m above sea level (median = 84.7 pmol/l; $p < 0.01$) (131).

3.4 Fetal and Neonatal Conditions

There are many authors who published articles about different forms of congenital hyperinsulinism and mutations in various genes that lead to this metabolic state (132) but to the best of knowledge none of these published results, that have been reproduced or verified by others. That may be due to the rarity of those mutations and syndromes and some of them also only manifest after a few months of life like the hyperinsulinism/hyperammonemia syndrome (133-135). The more important and better-researched syndromes are presented below.

3.4.1 Neonatal Blood Pressure

Elevated blood pressure is seen in offspring of diabetic but also of non-diabetic mothers and there seems to be a connection between cord insulin and C-peptide levels and especially the systolic blood pressure of the infant (Table 13) (136).

	Systolic blood pressure		Diastolic blood pressure	
	< 71 mmHg n = 62	≥ 71 mmHg n = 63	< 44 mmHg n = 60	≥ 44 mmHg n = 65
C-peptide (nmol/l) 95% CI	0.22* (0.20–0.25)	0.28* (0.26–0.30)	0.23*** (0.21–0.26)	0.26*** (0.23–0.28)
Insulin (pmol/l) 95% CI	316.7** (275–366.7)	437.5** (379.2–504.2)	366.7*** (320.9–404.2)	370.9*** (312.5–441.7)

Table 13 Different neonatal cord blood concentrations of insulin and C-peptide depending on the systolic and diastolic blood pressure (136)
Insulin and C-peptide show geometric mean (95% confidence intervals = CI), * = p < 0.05, ** = p < 0.001, *** = p > 0.05 (p-values state the significance of the correlation between the neonatal blood pressure and neonatal insulin/ C-peptide levels)

3.4.2 Erythroblastosis Fetalis (EBF)

The clinical picture of EBF is an increased amount of red blood cells in the peripheral blood (137). Cord blood insulin is markedly raised in infants with EBF compared to healthy newborns: 205.6 (± 35.4) pmol/l vs. 70.1 (± 15.3) pmol/l ($p < 0.01$, n = 12 EBF/ 14 control) (94, 137, 138).

Those differences are still remaining hours after birth (139) and insulin is also measurable in the neonatal urine, which shows similar results like those presented above. Infants with EBS have markedly raised urine insulin concentrations compared to healthy neonates (140).

3.4.3 Infant Respiratory Distress Syndrome (IRDS)

Newborns suffering from IRDS show a higher umbilical plasma cord insulin concentration than healthy newborns (141). Those results remain significant after adjusting for maternal oral glucocorticoid therapy before birth.

It remains unclear though if the neonatal hyperinsulinemia is induced by IRDS or the other way around e.g. because of maternal diabetes leading to neonatal hyperinsulinemia (142, 143).

3.4.4 Persistent Hyperinsulinemic Hypoglycemia of Infancy (PHHI/ Nesidoblastosis)

The reason for this disease is an abnormal development of the fetal pancreas *in utero* that leads to an overproduction of insulin (144, 145).

The mean umbilical cord insulin of neonates diagnosed with PHHI is higher compared with healthy control subjects: 199.3 (± 22.8) pmol/l vs. 47.2 (± 9.0) pmol/l ($p < 0.01$, n = 6 PHHI/ 12 control) (146).

3.4.5 Leprechaunism

This disease, also known as Donohue Syndrome, is caused by autosomal recessive mutations in the insulin receptor gene, which leads to extreme hyperinsulinism in the neonate (147-151).

These results are extracted from case studies, mainly focusing on different insulin receptor gene mutations, reporting the same outcome of elevated insulin concentrations in newborns with features of leprechaunism.

To the best of knowledge there are no consistent studies with cohorts, big enough to reach significance, concerning insulin levels at birth and Donohue Syndrome.

3.4.6 Beckwith-Wiedemann Syndrome (BWS)

BWS is an overgrowth syndrome that can also affect the pancreatic B-cells leading to hyperinsulinemia and potentially life-threatening hypoglycemia (152). Less is known about the exact mechanisms and, mostly transitory, hyperinsulinemia only seems to be present in about half of the cases (153).

Different case reports give no or different values and times of measured insulin: 205.6 pmol/l (2nd day *post partum)* (154), 68.4 pmol/l (at day 4 of life, measured in plasma) (155), 17.4 pmol/l (immediate neonatal period) (155)*;* children that developed hyperinsulinemia (no insulin values given): after 1.5 hours (156), within 24h *post partum* (157). No further data about exact time and measurement technique given.

3.4.7 Sotos Syndrome and Kabuki Syndrome

Both of them only sometimes cause hyperinsulinism and, if so, it usually only shows 1 to 3 hours after birth. In comparison to healthy infants, syndromic infants showed elevated insulin levels of approximately 50.0 pmol/l compared to healthy control subjects with only approximately 18.8 pmol/l (158). The samples were not taken straight after birth and not from the umbilical cord vessels.

Syndrome	Effect	Neonatal birth weight/ gestational age at the time of delivery	Sources
Leprechaunism	Hyperinsulinism at 4.5 months of age	1.7 kg/ term	(149)
	Hyperinsulinism at 5 days after birth	2.4 kg/ 40 weeks	(148)
Beckwith-Wiedemann Syndrome	Elevated blood insulin within the first 4 days of life	3.8 kg/ 38 weeks (median of all found cases)	(155, 156, 158)
Sotos Syndrome	Hyperinsulinism occurring at 30 min – 1 day after birth	3.5 kg/ 39+3 weeks (median)	(158)
Kabuki Syndrome	Hyperinsulinism occurring at 30 min – 25 days after birth	3.2 kg/ 37+2 weeks (median)	(158)
Russell-Silver Syndrome	No effect on neonatal insulin levels described	-	-
Hyperinsulinemia and Hyperammonemia Syndrome	Elevated blood insulin and ammonium at 6 months of age and older	3.5 kg/ term (patient 1), 2.2 kg/ term (patient 2)	(159)
		2.2 kg/ term	(160)
			(134, 135)

Table 14 Overview of syndromes possibly influencing neonatal and infantile insulin levels
The table summarizes literature findings in the period of 1952 until July 2018

4 Discussion

The fact that maternal diabetes, either type 1, type 2 or gestational diabetes mellitus, influences the fetal and neonatal insulin production is widely known and the mechanisms seem to be understood.

Though there are other causes mentioned in this thesis, these are often speculative. With many of them, it is not quite clear in what relation they are to the neonatal cord insulin concentration after birth, i.e. whether they are the cause or consequence of altered neonatal insulin or just coincidental findings.

4.1 Overall Factors Influencing the Neonatal Cord Hormone Level

All studies have to be viewed cautiously due to some overall problems and possibilities of bias mentioned below.

The number of participants, study method and p-values has to be taken into account when evaluating the significance of different studies. Some authors do not always state all the parameters needed for statistical expression, like standard deviation, standard error, p-value, number of participants and thorough description of figures and tables. Because of that it is sometimes difficult to evaluate the significance and reliability of the study.

Furthermore it is difficult to examine one isolated feature without being influenced by other circumstances e.g. when testing the relevance of the fetal sex, the influence of maternal or neonatal features and diseases, environmental factors, maternal lifestyle etc. has to be controlled to get a valid result. As this is nearly impossible, most of the conducted studies have to be seen with reservations.

An additional factor making it difficult to compare studies with each other is the different methods used to measure hyperinsulinemia. Insulin, c-peptide, proinsulin and 32-33 split proinsulin are all mirrors of the neonatal pancreatic function, but measurement techniques are different. Especially in older studies laboratory

methods were not as developed and it was impossible to immunoassay c-peptide and proinsulin specifically (161). The time of blood collection and processing of the sample could also be an influencing factor.

Within studies it does not have an impact on the results, because the techniques remain the same for different aspects of research, but it makes it more difficult to compare studies with each other (162, 163).

As often mentioned below, sometimes it cannot be clear or is possibly misinterpreted if the elevated insulin levels are caused by some sort of influence or the reason of something, meaning that the cause and the effect of neonatal hyperinsulinemia are often confused with each other.

Elevated neonatal blood pressure for example is likely to be caused by hyperinsulinemia rather than the newborn being hyperinsulinemic, because of the elevated blood pressure. It may also be not causally related at all or both symptoms are the manifestation of the same underlying condition.

Of course many factors mentioned in this thesis cannot be influenced by insulin or are well researched to be a cause, such as the fetal sex or the effect of maternal diabetes on neonatal insulin, but some have to be interpreted with caution. For this reason it also has to be considered if the study outcomes and measured values are adjusted for other possible confounding factors such as maternal lifestyle or environment.

Interestingly, insulin secretion seems to follow a circadian rhythm (164). It is not researched if that plays a role in fetal insulin levels straight after birth, but no study mentioned in this thesis, took the time of day of birth into account.

4.2 Aspects of Perinatal Modifiers of Insulin in the Newborn

Girls having higher *post partum* cord insulin concentrations than boys is not a uniform finding, which can be due to overall influencing factors (see section 4.1) although study population numbers are big and a significance with $p < 0.05$ was always given. A reason for female neonates having higher insulin concentrations than males could be that females are more insulin resistant *in utero* (50, 52, 55).

Taking a look at older children, girls at 5 years of age are more insulin resistant than boys too (165), supporting this hypothesis and suggesting that there could be a genetic or epigenetic cause to insulin resistance.

Within modes of delivery a falsifying factor could be that the majority of women delivering with instrumental assistance receive intravenous dextrose containing oxytocin to strengthen contractions. Higher cord insulin levels could be due to the effect of the medication and not to the mode of delivery itself (8, 120).

Another aspect is that not all authors are in unison about neonatal insulin levels in assisted vaginal deliveries. Supporting the statement that cord insulin is higher in assisted vaginal delivery is the larger numbers of participants in studies showing this effect. However, it is difficult to prove that hyperinsulinemia arises because of the mode of delivery and was not already present days to weeks before birth (58).

The disparity in cord insulin concentrations in newborns delivered by elective caesarean section compared to those born via emergency section could be explained by the degree of neonatal stress. An elective caesarean section is a non-stressful event compared to labor leading to an emergency C-section or a vaginal delivery, assisted or not, where the neonatal catecholamine levels are higher leading to a bigger subsequent drop of insulin (57, 58).

Also neonatal cortisol levels are influenced by the mode of delivery. Neonates delivered by Caesarean section show lowest levels of cortisol and those born by assisted vaginal delivery show highest amounts of cortisol, measured in the umbilical cord vein or saliva of the newborn (166-168). This is, however, contradictory to the findings that insulin levels are highest in newborns delivered by Caesarean section. Because if we take into account that oral glucocorticoids do increase the neonatal C-peptide levels, endogenous cortisol also should have an insulin and C-peptide increasing effect on the neonate.

Like in other sections, cause and effect are unclear, i.e. if the mode of delivery causes a rise in the fetal insulin level or if the raised fetal insulin level leads to a higher rate of caesarean section e.g. due to macrosomia, or to fetal vital instability during vaginal delivery (58, 63).

Unfortunately, there are very few studies looking into neonatal insulin and ethnicity making it difficult to evaluate if the results are real findings demonstrating ethnic influences on neonatal cord insulin levels or only coincidental. It is known that members of certain ethnic groups are more prone to get type 2 diabetes. This is the case in Polynesian, Indian and South Asian people (169-172). It is likely that, like in Indian newborns, differences in the insulin concentrations are already measurable straight after birth, but it is not quite explainable why this is not the case in others e.g. South Asians. However, as already discussed, there are many other factors influencing the insulin concentrations in the neonatal cord blood like maternal lifestyle, dietary factors or the genotype.

The problem in linking neonatal hyperinsulinemia with weight and body composition is that the biggest risk factor for the birth-weight being > 90th centile is maternal diabetes which, as discussed before, also leads to elevated insulin concentrations in the newborn (173). So it can be assumed that fetuses of diabetic mothers have a different growth pattern than the ones of metabolic healthy mothers. They suffer from growth retardation due to placental incompetence during the first 20 weeks and experience a growth spurt in the third trimester due to their hyperinsulinemia as a result of maternal hyperglycemia (78, 90, 174).

In addition, the results of the twin studies strengthen the assumption that neonatal insulin concentrations depend on the metabolic environment of the mother rather than the twin's weight. It is likely that the hyperinsulinemic and, at the same time, heavier fetus gets more glucose from the mother and develops this metabolic state because of its oversupply with glucose *in utero*.

The reason for higher insulin concentrations in premature born neonates probably reflects the action of insulin as a growth factor (175). The exact mechanisms of insulin acting as a growth factor are not fully understood but it is assumed that insulin can bind to the same receptors as the insulin-like growth factors (176). Even stronger evidence for insulin acting as a growth mediator *in utero* is the clinical picture of infants born to diabetic mothers. Maternal diabetes is, as presented in section 3.2.1, accompanied by fetal and neonatal hyperinsulinemia. Neonates of diabetic mothers also tend to have more body fat

and to be macrosomic (>4000g) more often, which supports the role of insulin as a growth factor.

Furthermore there is the possibility of insulin receptors being underdeveloped at a very young gestational age leading to tissue insulin resistance and in turn higher insulin production. This was found in animal models (177).

4.3 Parental Influences on the Neonatal Insulin Concentrations and its Possible Misinterpretations

Maternal Diabetes is the most important and most common reason for neonatal hyperinsulinemia and hypoglycemia. The pathophysiological mechanism is well described (see Introduction) and there do not seem to be discrepancies among researchers.

One paper reported on offspring of mothers with gestational diabetes having higher cord insulin values than newborns of type 1 or type 2 diabetic mothers (88). That may be due to the relatively small number of participants (n = 105) in comparison to the bigger studies (n > 170) that concluded the opposite (84, 85, 93). Nevertheless all types of maternal diabetes (GDM, type 1 and type 2 diabetes mellitus) lead to neonatal hyperinsulinemia and have to be detected and treated.

Interestingly, other factors influencing the neonatal inulin after birth, mentioned in this thesis regarding non-diabetic women, are also associated with a difference in offspring of diabetic mothers. Newborns of obese mothers, born by an elective cesarean section and female neonates also show higher cord insulin levels in diabetic mothers. So it seems that those factors such as the mode of delivery or the fetal sex are causing neonatal hyperinsulinemia independent of diabetes mellitus.

Stunningly, boys seem to be more influenced by altered maternal glucose tolerance than girls leading to the assumption that, despite girls having “naturally” higher insulin levels at birth, boys are more vulnerable to metabolic changes in the mother (56) and males have to have a slightly higher risk of developing diabetes in their adolescence (178). On the other hand mothers carrying a boy are also more

prone to develop gestational diabetes (179). All of this taken into account suggests that males do react differently to the maternal metabolic environment than females, and may have lower capacities to adjust to environmental changes.

Most studies ruled out maternal diabetes as confounding factor when looking into other causes for neonatal hyperinsulinemia, but a normal oral glucose tolerance test (OGTT) at weeks 24 - 28 is no prove of the mother not having a disturbed glucose metabolism. The so-called "*glucose steal phenomenon*" describes the possibility of a flux of glucose between the mother and the fetus, as glucose is able to cross the placenta. The higher the maternal blood glucose, the more glucose is "stolen" by the fetus. The result of this glucose steal is not only that the fetus becomes hyperglycemic and hyperinsulinemic, but also that the maternal blood glucose may stay within normal ranges and the women presents with a non-pathological OGTT (21). Because of this a maternal disturbance of glucose homeostasis can remain undetected and unmanaged and the neonate develops the same features as offspring of mothers with fully distinct and unmanaged diabetes. One study, examining maternal OGTT results in dependency of amniotic fluid insulin levels in women suffering from gestational diabetes, showed that the higher the amniotic fluid insulin levels the lower the OGTT results (180). That supports the hypothesis that some cases of GDM, which could be diagnosed by an amniotic fluid insulin measurement, stay undetected because of a masked normal OGTT.

Furthermore, screening protocols for GDM differ by country, which also leads to adverse pregnancy outcomes like neonatal macrosomia due to the lack of treatment of the mother (181-183).

Considering those possibilities of undetected maternal diabetes, it is often difficult to be sure that proper adjustments were made in the study.

How diabetic control and management with different modalities influence the neonatal cord insulin concentration needs to be researched more thoroughly. There are very few studies addressing this topic and most of them do not have a uniform study design to allow comparison. This makes it difficult to draw a valid conclusion and all outcomes mentioned in this thesis have to be seen with reservations.

Researchers are in unison about the influence of maternal obesity on neonatal insulin levels. The higher the maternal BMI, the higher is the neonatal insulin and also the risk for adverse pregnancy outcomes like macrosomia, shoulder dystocia, hypoglycemia and more rises (90). Also the risk for developing gestational diabetes and in turn the risk for fetal hyperinsulinemia at birth, are increased even stronger. This is a problem we have to bear in mind, as more and more women, especially those living in more developed countries, are obese (4, 184). Especially obesity combined with maternal diabetes is a great risk factor to the neonate.

It is difficult to evaluate the impact of maternal diet and lifestyle on the newborn as those parameters are not easy to measure and in most cases were not objectively measured but based on self-report by the study participants. Hence, the reliability of the studies are very much influenced by the mothers' honesty and compliance to the study and its rules.

Furthermore, the reliability of the presented study about maternal carbohydrate intake and physical activity is questionable. Not only is it the only study presenting data about maternal diet and physical activity influencing the neonatal glycemia after birth, but also are the presented data confusing. It is not clear if the study presents a hypothesis or if the statement, that a high-carbohydrate intake (> 75% of calories) and less than 40min of moderate physical activity within 24h *ante partum,* is based on facts. There needs to be more research done on the field of maternal lifestyle influencing neonatal insulin levels.

Not only the maternal diabetic state, but also paternal insulin resistance seems to have influence on neonatal insulinemia at birth. Unfortunately, there is only one study regarding this topic available on public databases. Within this study some important numbers and descriptions are missing to fully understand the impact of paternal factors on the neonate, such as a thorough description of the paternal HOMA-IR and further information about the tertiles used to stratify the data in Figure 13,. However, the study was included because it seems only logical that if fetal genetics composes of both biological parents, the child's body composition and hormone concentrations before, at and after birth are also influenced by both parents.

4.4 External Influences Likely to Affect Neonatal Insulin Concentration

There is not much research about the impact of different pharmacologic treatment given to the mother *ante partum* and all of the studies presented in this thesis need to be verified furthermore to provide reliable data.

The outcome that neonatal insulin levels rise when the mother is infused with a glucose solution *ante partum* is a uniform finding and mechanistically plausible due to the ability of glucose to cross the placenta and thus causing a subsequent rise in fetal insulin to maintain normoglycemia.

Environmental factors like air pollutants seem to influence the neonatal insulin levels at birth, but this topic is also lacking more and specific literature. There are a few animal studies examining the impact of organophosphates on non-human fetuses, supporting findings in humans (185, 186).

An additional compromising factor on the notion of air pollutants influencing the neonatal insulin production is, that the quality of air was only measured at the participants' home and not at their work or other places they visit regularly. This makes it impossible to estimate the total load of air pollutants on the test subjects. However, like for organophosphates, more research is needed to support the hypothesis that the risk for childhood diabetes and altered insulin sensitivity in healthy adults is increased when there is a higher degree of particulate air pollution (187-189).

4.5 Fetal and Neonatal Conditions Interacting with the Cord Insulin Level

It is controversial whether insulin has an action on the sympathetic nervous system and if, by stimulating this, inducing a rise in blood pressure (190). However, it is more likely that hyperinsulinemia is the underlying cause for hypertension and not the other way around.

The major problem with fetal and neonatal disease and its impact on neonatal insulin levels at birth is that many of these conditions have a low prevalence and are also poorly researched. Pathophysiologic mechanisms are not fully understood and, as mentioned before, the numerous other, possible influencing factors have to be taken into account when it comes to neonatal hyperinsulinism.

5 Conclusion

This thesis gives an overview of different conditions and factors associated with neonatal hyper- or hypoinsulinism. It is very important to bear them all in mind when it comes to avoiding harmful consequences of hyperinsulinism such as possibly life threatening neonatal hypoglycemia and subsequent brain damage.

An important factor influencing the neonatal pancreatic activity is maternal obesity. Maternal obesity not only alters the neonatal insulin levels but also the maternal metabolism itself, elevating the risk of the mother developing GDM or type 2 diabetes. Healthcare professionals and women in risk need to be aware of the consequences of maternal obesity and need to be managed appropriately, if possible, before they develop diabetes.

Maternal diabetes, either type 1, type 2 or gestational diabetes is the most important and best researched factor influencing neonatal insulin concentrations at birth. This may also be the underlying cause for many other suspected insulin-altering factors and has to be detected and managed early and accurately to prevent neonatal hypoglycemia and further adverse pregnancy outcomes and damage.

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