Diploma Thesis

MATERNAL AND FETAL SERUMLIPOPROTEINS IN GESTATIONAL- AND TYPE- I DIABETES

Submitted by

Chahira Moussa

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Clinic of Obstetrics and Gynecology

Auenbruggerplatz 14, 8036 Graz, Austria

First supervisor

Mag. Dr. rer. nat Christian Wadsack

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Affidavit

Herewith I, Chahira Moussa, declare that I have written the present diploma thesis fully on my own and without any assistance from third parties.
Furthermore, I confirm that no sources have been used in the preparation of the thesis other than those indicated in the thesis itself.

Graz, June 2009 *Chahira Moussa*

Acknowledgement

I am particularly grateful to my supervisor **Mag. Dr. rer. nat Christian Wadsack** for the excellent support. He made a lot of efforts to support me in writing this thesis. With his friendly and patient manner he always offered me advice.

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Abstract

Purpose: The few existing studies on lipoprotein metabolism during pregnancy devoted, that dyslipidemia occurring during pathological pregnancy leads to an excess of fetal growth. The aim of this thesis is to compare and to discuss different studies regarding alterations in maternal and fetal lipid and lipoprotein profiles in women with gestational diabetes or type I diabetes compared to healthy women with normal glucose tolerance. The main focus of attention in this paper work is to depict varieties in maternal and fetal lipoprotein profile and to extract methodological differences between the selected studies.

Methods: This thesis illustrates the results of an extensive pubmed literature search concerning this topic. Changes in serum lipid, lipoprotein and apolipoprotein concentrations during and after pregnancy in control and in diabetic woman as well as in newborns of normal and diabetic mothers were summarized, analyzed and discussed. I investigated eighteen papers, which show relevant subject area. A systemic research of following enzymes revealed no hits: apolipoprotein E, non-esterified fatty acids, HDL- cholesterol ester, different lipases and enzymes (Acyl- CoA: cholesterol transferase, Lecithin: cholesterol transferase). Therefore these named molecules where not discussed further on.

Results: The results of the interpretation show a continual elevation in total cholesterol, LDL- cholesterol and triglyceride concentrations in non diabetic mothers from the first to the third trimester of pregnancy which is consistent over all studies. In general patients with gestational diabetes and type I diabetes mellitus show lower total maternal cholesterol and LDL- cholesterol levels during the second as well as during the third trimester compared to age matched controls. Compared to non diabetics, a significant elevation in triglyceride concentrations in diabetic women was detected. Analyses of the studies related to HDL- cholesterol revealed no alterations in HDL- cholesterol concentration during gestation in normal or pathological pregnancies. A postpartum decrease in lipids and lipoproteins are observed in all studies, which we compared. The differences in measured maternal lipid and lipoprotein concentrations between some studies

may be caused by be different mode of sample storage, frequently thawing and freezing of the samples and different analytical methods, which the authors used. However, comparison of the studies, which measured cord blood serum cholesterol, TG and lipoprotein concentrations, revealed no significant differences in the measured values. Furthermore, no significant differences in total cholesterol, LDL- cholesterol, HDL- cholesterol and triglycerides in newborns of diabetic mothers compared to newborns of nondiabetic mothers could be observed. These results can be explained by a relatively good maternal metabolic glycemic control and a strictly maternal blood glucose monitoring throughout pregnancy.

Conclusion: Before making a general statement regarding lipid and lipoprotein management during pregnancy once has to verify study protocol, methods and sample size. A remarkable difference in methods between all studies was the different analytical methods, which the authors used. To achieve homogeneous parameters, standardisation in analytical methods is desirable. The studies should consider the type of diabetes mellitus, the degree of metabolic control and the ethnic origin in pregnant mothers in one hand as well as the gender and body weight of their neonates on the other hand.

Keywords: Lipoproteins; apolipoproteins; gestational diabetes mellitus; type I diabetes mellitus; mothers; newborns

Zusammenfassung

Zielsetzung: Die wenigen bekannten Studien zum Lipoprotein- Metabolismus während der Schwangerschaft besagen, dass die durch pathologische Schwangerschaften auftretende Dyslipidämie zu einem erhöhten fetalen Wachstum führt. Ziel dieser Diplomarbeit ist es, verschiedene Studien hinsichtlich der Änderungen im mütterlichen und fetalen Lipid- und Lipoproteinprofil bei Frauen mit Gestationsdiabetes oder Typ I Diabetes mellitus, verglichen mit gesunden Frauen, gegenüberzustellen und zu diskutieren. Ein vorwiegendes Augenmerk dieser Arbeit ist es, Unterschiede im mütterlichen und fetalen Lipoproteinprofile anzuführen und etwaige Unterschiede, in Analysemethoden und Dateninterpretationen zwischen den ausgewählten Studien zu beschreiben und festzuhalten.

Methoden: Diese Diplomarbeit zeigt die Ergebnisse einer ausgedehnten Literatursuche und Literaturanalyse in pubmed. Änderungen in Serum Lipid-, Lipoprotein- und Apolipoprotein- Konzentrationen bei Schwangeren, mit und ohne Diabetes als auch bei Neugeborenen von Nichtdiabetikerinnen und Diabetikerinnen wurden zusammengefasst, analysiert und diskutiert. Achtzehn Studien zu besagter Problematik wurden miteinander verglichen. Die Suche nach folgenden Enzymen und Proteinen ergab keine Treffer (bei Mutter und Feten) und sie konnten somit nicht miteinander diskutiert werden: Apolipoprotin E, nicht-veresterte Fettsäuren, Lipasen, Enzyme (wie Acyl- CoA: Cholesterol Transferase, Lecithin: Cholesterol Acyltransferase).

Ergebnisse: Die Ergebnisse der Auswertung zeigen in allen Studien einen kontinuierlichen Anstieg in Total- Cholesterin-, LDL- Cholesterin- und Triglycerid-Konzentrationen in gesunden Frauen vom ersten zum dritten Trimester. Dagegen zeigen Schwangere mit Gestationsdiabetes und Typ I Diabetes geringere Total-Cholesterin- und LDL- Cholesterin Werte während des zweiten und dritten Trimesters im Vergleich zu ihren Kontrollen. Verglichen mit nichtdiabetischen Schwangeren zeigen Schwangere mit Diabetes deutlich erhöhte Triglycerid-Konzentrationen. Eine Analyse der Studien bezüglich der HDL- Cholesterin-Konzentrationen zeigte sowohl in normalen als auch in pathologischen

Schwangerschaften keine Änderungen. Eine postpartale Reduktion der Lipid und Lipoproteine wurde in allen Studien beobachtet. Die Unterschiede in den gemessenen mütterlichen Lipid- und Lipoprotein- Konzentrationen zwischen einigen Studien könnten durch verschiedene Lagerung der Serum- und Plasmaproben, häufiges Auftauen und wieder Einfrieren dieser Proben und durch unterschiedliche analytische Methoden, die die Autoren verwendeten, hervorgerufen worden sein. Der Vergleich aller Studien, die fetale Serum-Cholesterin-, Triglycerid- und Lipoprotein- Konzentrationen gemessen haben, ergab keine signifikanten Unterschiede. Weiters konnten im Vergleich zu Neugeborenen gesunder Mütter keine Unterschiede in Total Cholesterin-, LDL-Cholesterin-, HDL- Cholesterin- und Triglyceride- Werten von Neugeborenen diabetischer Mütter gefunden werden. Diese Ergebnisse könnten auf die relativ aussagekräftigen Blutzuckerkontrollen und auf das strikte Monitoring während der Schwangerschaft zurückzuführen sein.

Zusammenfassung: Um eine generelle Beurteilung der Änderungen in Lipid- und Lipoprotein- Konzentrationen durchzuführen, müssen Studienprotokolle, Methoden und die Größe des Patientenkollektivs überprüft werden. Ein beachtenswerter Unterschied zwischen allen Studien waren die unterschiedlichen analytischen Methoden, die die Autoren zu Messung der Blutfette verwendeten. Diese verschiedenen Analysemethoden zeigen insbesondere auf der mütterlichen Seite zum Teil signifikante Unterschiede in den gemessenen Lipoproteinfraktionen. Eine Standardisierung, um homogene Parameter zu erhalten, wäre erstrebenswert. Die Studien sollten den Diabetes Typ, das Maß der Blutzuckerkontrollen und den ethnischen Ursprung der Schwangeren auf der einen Seite und das Geschlecht und das Geburtsgewicht der Neugeborenen auf der anderen Seite berücksichtigen.

Schlagwörter: Lipoproteine; Apolipoproteine, Gestationsdiabetes; Typ I Diabetes mellitus; Mütter; Neugeborene

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Glossary and abbreviations

ACAT	Acyl- CoA : cholesterol transferase
ADA	American Diabetes Association
apoA- apoH	Apolipoproteins
CETP	Cholesteryl ester transferase protein
EL	Endothelial lipase
FFA	Free fatty acids
GCT	Glucose challenge test
GDM	Gestational diabetes mellitus
HDL	High- density lipoprotein
HDL- CE	HDL- cholesteryl ester
HSL	Hormone sensitive lipase
IDDM	Insulin dependent diabetes mellitus
IDL	Intermediate- density lipoprotein
LCAT	Lecithin : cholesterol acyltransferase
LDL	Low- density lipoprotein
LPL	Lipoprotein lipase
VLDL	Very low- density lipoprotein
NDDG	National Diabetes Data Group
NEFA	Non- esterified fatty acids
OGTT	Oral Glucose Tolerance Test
TC	Total cholesterol
TG	Triglyceride

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1 Introduction

1.1 Lipids and lipoproteins

Lipids are hydrophobic molecules which can synthesized either by the cells itself (endogenous lipids) or derived from dietary fat (exogenous lipids). Lipids have a broad range of biological functions e.g. part of the cell membrane and responsible for the barrier permeability and major source of stored energy in adipose tissue as well as participating as important signalling molecules. Lipids originate entirely or in part from two distinct types of biochemical subunits, in particular from ketoacyl and isoprene groups. Depending from the origin lipids can be divided into different categories: sterols, waxes, glycerolipids, sphingolipids and fatty acids.

1.1.1 Fatty acids

The common backbone structure molecule for most of the different types of lipids is the fatty acid chain. Fatty acids are long- chain hydrocarbon molecules ending with a carbonic acid group. The hydrocarbon chain forms the hydrophobic part, whereas the carboxyl group is part of the hydrophilic structure of the molecule. The Fatty acids can be saturated or unsaturated, depending whether the backbone contains double bonds. Figure 1 depicts a stearic acid, which belongs to the group of saturated fatty acid whereas the oleic acid contains one double bond (1).

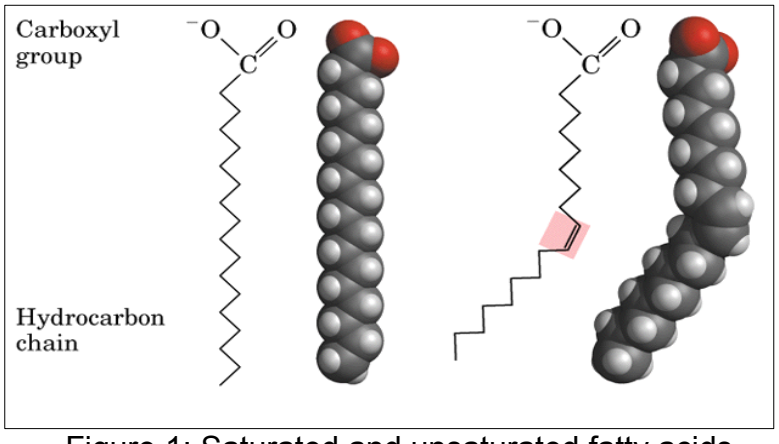


Figure 1: Saturated and unsaturated fatty acids

Another common form of fatty acid classification is depending if they are essential or non-essential. Polyunsaturated fatty acids, which contain double bonds beyond carbon 9, are called essential fatty acids. Essential fatty acids cannot be synthesized within the human organism therefore they are originated by food intake.

Free fatty acids are in general water insoluble hence, they are not able to penetrate the plasma membrane or to be part of the human plasma in its free form. Therefore, free fatty acids must be bound to albumin or other transport proteins for carrying around the body. Usually free fatty acids result from the breakdown of a triglyceride molecule to the components of fatty acids.

Fatty acids are stored as triglycerides, which is the major form of energy source in human organism. In the lipid bilayers, which contain amphipathic phospholipids, fatty acids build the main structural component in which built cellular plasma membranes and the intracellular membranes of organelles (Figure 2 and 3) (2).

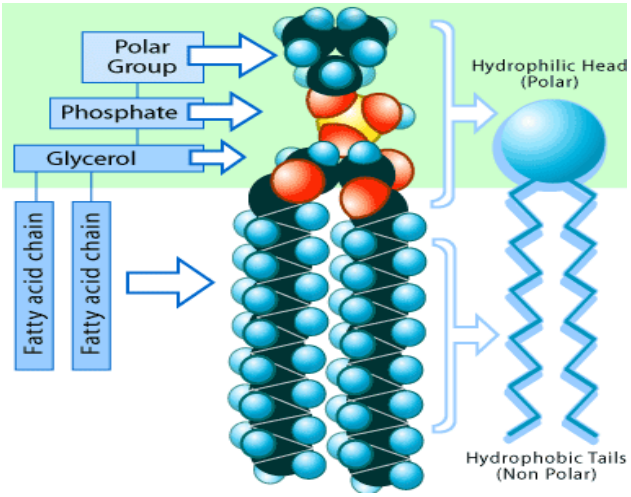


Figure 2: Structure of a phospholipid

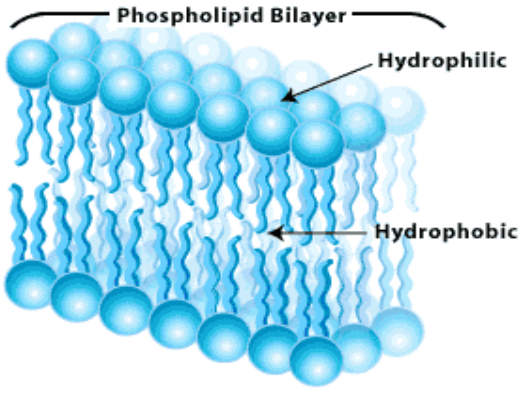


Figure 3: Scheme of a lipid bilayer

1.1.2 Lipoproteins

In order to transport lipids in aqueous circumstances, in particular in blood, soluble complexes called lipoproteins are formed. Plasma lipoproteins are spherical particles composed of a hydrophobic lipid core surrounded by a hydrophilic layer made of proteins, which surrounds the lipid particles and make it soluble.
The lipid core contains triglycerides and cholesteryl esters, small amounts of other fatty acids compounds, such as phospholipids, unesterified cholesterol, and specialized proteins, called apolipoproteins. These proteins facilitate lipid solubilization, help to maintain structural integrity of lipoproteins and are primarily synthesized in the liver and the intestine. They also serve as enzyme co- factors and receptor ligands that regulate the metabolism of lipoproteins and their uptake in tissues. There are six major classes of apolipoproteins with several subclasses described in the literature: apo A (apo A-I, apo A-II, and apo A-V), apo B (apo B48 and apo B100), apo C (apo C-I, apo C-II, apo C-III, and apo C-IV), apo D, apo E and apo H.

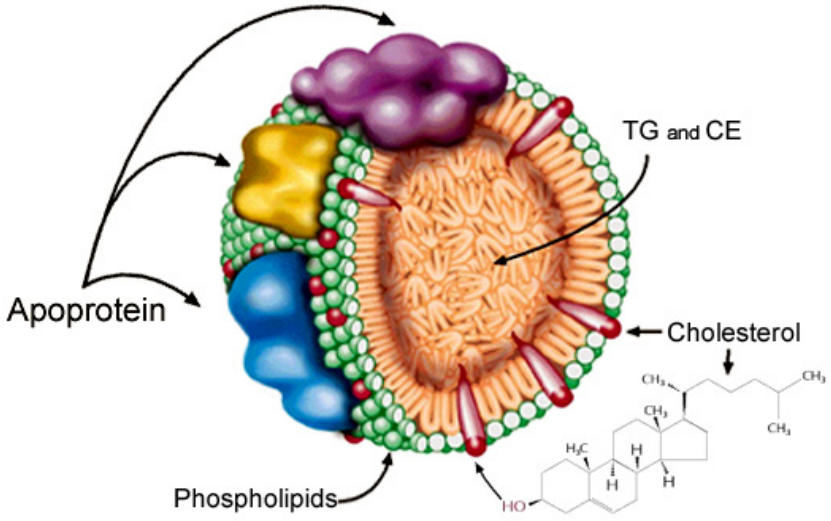


Figure 4: Schematic illustration of a lipoprotein particle

As depicted in Figure 4, amphiphatic molecules, which compose the outer layer of lipoproteins are specifically arranged. The central core is composed by the hydrophobic part, whereas the hydrophilic region faces the surrounding aqueous environment (3).

1.2 Lipid metabolism

For energy metabolism in humans of three different sources can be provided by fatty acids: firstly fatty acids embedded in triglycerides, secondly triglycerides synthesized in the liver and secreted as well as triglycerides stored in adipocytes as lipid droplets.

Lipids coming from dietary origin cannot be absorbed by the intestine. Therefore, they are processed by intestinal epithelial cells and then secreted into the bloodstream as part of large, fat rich lipoproteins called chylomikrons. On their way to the liver, chylomicrons pass through endothelial capillaries, lose some fat, and their remnants are taken up by the liver cells. In the liver, the lipids obtained from chylomikron remnants are re- processed and then secreted back into the blood stream as part of VLDLs. Depletion of fat from VLDL transform the particle into an IDL, which upon further degradation of its fat is converted into a relatively stable particle, called LDL.

HDL transports excess cholesterol mostly to the liver by direct and indirect pathway. The most relevant pathway is the indirect one, which is mediated by CETP. Cholesteryl ester can be transferred by the action of the CETP in plasma to VLDL in exchange for triglyceride. The cholesteryl ester can then be returned to the liver as VLDL and/or LDL particles are taken up by it (4).

Density (g/ml)	**Class**	Diameter (nm)	% protein	% cholesterol	% phospholipid	% triacylglycerol
>1.063	HDL	5-15	33	30	29	8
1.019-1.063	LDL	18-28	25	50	21	4
1.006-1.019	IDL	25-50	18	29	22	31
0.95-1.006	VLDL	30-80	10	22	18	50
<0.95	Chylomikrons	100-1000	<2	8	7	84

Table 1: General characteristics of plasma lipoproteins

The main characteristics of lipoproteins are summarized in Table 1 (5).

Out of the five lipoproteins, chylomikrons are once with highest amount of triglycerides. VLDL contains more triglyceride than cholesterol. As the triglycerides

are removed for energy or storage, the VLDL remnants continue to circulate as LDL particles. About 50% of serum cholesterol is carried by LDL particles. HDL particles contain more than one quarter of serum cholesterol.

Clinical practice has traditionally been based on the concentration of cholesterol in the plasma. Along to the daily cholesterol intake, all the cells in the body can synthesize cholesterol endogenously, although most of the synthesis is centralized in the liver. The ability to synthesize cholesterol by cells is essential for building up cell membranes and as a precursor for steroid hormones and for uptake of vitamins (6, 7).

1.3 Lipid and lipoprotein changes in pregnancy

1.3.1 Normal pregnancy

Generally, concentrations of all lipoprotein fractions increase over progress during pregnancy (8). Several authors tried to study mechanisms, which cause these lipoprotein alterations in pregnant women. The increase in lipoprotein subclass concentrations represent either increased synthesis or reduced catabolism.
An increase in the triglycerides occurring during gestation has several reasons, one of them is the increase in circulating VLDL concentrations. This VLDL concentration change only becomes significant at the third trimester of gestation, coincide with the decline in postheparine lipoprotein lipase activity (around 50%) (9), which suggests that the enzyme activity and circulating VLDL may be related. There is also a maternal hypertriglyceridemia due to enhanced hepatic production of VLDL triglycerides under the effect of exaggerated oestrogen levels (10), as oestrogen treatment has been shown to enhance liver VLDL production (11).
The specific enrichment of LDL and HDL by triglycerides during gestation indicates that other factors besides those commented above may also contribute to the development of maternal hypertriglyceridemia. The reduction in postheparin hepatic lipase activity during the first trimester of gestation could decrease the conversion of triglyceride- containing HDL_{2b} into the smaller HDL_{3a}, and thus account for the specific relative increment of HDL_{2b}. HDL_2 are rich in triglycerides.

These changes are also probably triggered by the rising oestrogen concentration, which began at the first trimester of gestation (3; 12).
An additional factor that may contribute to the shift in HDL subclass distribution to HDL_{2b} particles could be LCAT activity, which has been reported to increase during pregnancy by Alvarez et al (11).
A reduced clearance of triglycerides due to decreased extrahepatic lipoprotein lipase activity is seen during late gestation. This change is caused by the insulin-resistant condition that normally takes place at this stage of pregnancy. Consequently, a surfeit of plasma free fatty acids is available as substrate for hepatic TG synthesis and secretion (as VLDL TG). Additionally, insulin resistance during pregnancy has been shows to produce a decline in lipoprotein lipase activity, and may result in decreased peripheral catabolism of VLDL TG (3; 5; 7).

1.3.2 Diabetic pregnancy

During pregnancy several studies have described altered lipid metabolism. Increasing insulin resistance in late pregnancy is considered to be responsible for the hypertriglyceridemia observed during “normal” pregnancy.

In women with diabetic pregnancy increased insulin resistance may account for a further rise in lipoprotein concentrations. Insulin resistant states are associated with an increase in VLDL production and postprandial chylomicronemia (13). A number of potential mechanisms could explain the inverse relationship between the hypertriglyceridemia of insulin resistant states and increased HDL catabolism leading to low plasma HDL concentration. One is a reduction in LPL activity, which would have the effect of impairing the maturation of HDL particles. In addition, the combination of CETP- mediated triglyceride enrichment of HDL coupled with the elevated hepatic lipase activity that occurs in insulin resistance enhances the remodelling of HDL in the circulation with an increased HDL catabolism as shown in Figure 5 (13).

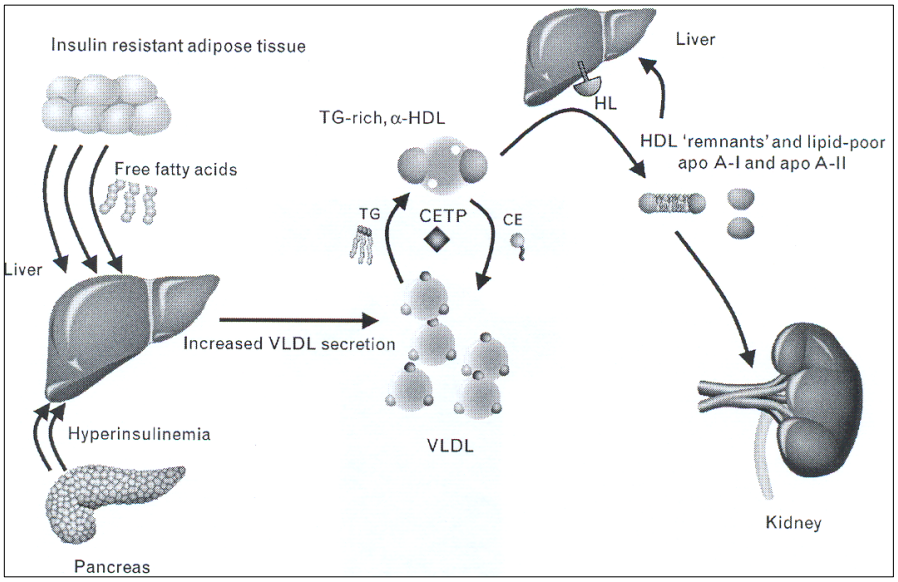


Figure 5: Mechanism for lowering the concentration of HDL- cholesterol in insulin-resistant state

Gestational hormone perturbations may be also a characteristic of diabetic pregnancy (14). Couch et al (14) detected elevated concentrations of plasma prolactin and progesterone in diabetic mothers. Additionally, plasma β-estradiol tended to be increased above normal in diabetic mothers. The relevance of this study is rooted in the finding that all three hormones affect lipoprotein triglyceride metabolism in pregnancy. Furthermore, oestrogen has also been shown to increase VLDL synthesis and reduced removal, and ultimately increased circulating VLDL TG. Prolactin seems to inhibit adipose tissue lipoprotein lipase while stimulating breast lipoprotein lipase in late gestation. Thus, the physiologic outcome of increasing concentrations of prolactin with advancing gestation could be explained by a shift in triglyceride storage from the adipocyte to the breast in preparation for lactation. With this tissue specific lipase shift, levels of circulating lipids, specifically FFA and triglyceride, may increase. In conclusion, elevated levels of gestational hormones in diabetic pregnancy could explain, in part, the lipid and lipoprotein perturbations demonstrated in women with diabetic women (14).

1.4 Lipid and lipoprotein changes in fetal circulation

1.4.1 Normal pregnancy

Fetal metabolism, and consequently fetal growth, directly depend on the nutrients crossing the placenta, and therefore the mother adapt her metabolism in order to support this continues draining of substrates. The mother develops hyperphagia from early gestation which, together with endocrine changes, allow her net body weight to be increased and such changes mainly corresponds to the accumulation of fat depots, which occurs during the first two- thirds of gestation. During the last trimester of gestation, maternal lipid metabolism switches to a catabolic condition. Adipose tissue lipolytic activity becomes enhanced as a consequence of an increase in activity of the hormone sensitivity lipase, the key enzyme for the lipolytic cascade.

It has been suggested that during early gestation, fetal lipids are derived from free fatty acids crossing the placenta, whereas in advanced gestation there is a gradual shift to de novo synthesis in fetal tissue.

Another metabolic adaption normally occurring during late gestation is the development of maternal hypertriglyceridemia. Maternal triglycerides do not directly cross the placenta but besides being a source of essential fatty acids for the fetus as a source of oxidative substrates. The ability of the placenta to extract fatty acids present in maternal plasma triglycerides to the fetus occurs to the presence of lipoprotein receptors and lipase activities in the placenta.

In consideration of the morphological characteristics of the human placenta, transfer of substances from maternal plasma to fetal plasma is dependent upon assimilation by trophoblastic cells and then deposition into the fetal circulation.

LDL- cholesterol appears to be taken up and degraded in the placenta by a saturable, receptor mediated process. The human placenta possesses minimal capacity for the de novo cholesterol synthesis, which is used for membrane formation, or steroid synthesis (15).

1.4.2 Diabetic pregnancy

Over the last years diabetes is considered to be an important factor for altering maternal fat metabolism and complicating fetal development. Some studies have shown that a promoting transfer of lipids to the fetus by an increasing materno-fetal concentration gradient, especially of free fatty acids and triglycerides has a profound impact on fetal circulating lipids in pregnancy. The triglycerides are accumulated in the placenta with a higher degree in the diabetic group, indicating an enhanced fetal uptake to fulfil the energetic demands, growth and fat storing deposition of the fetus. Maternal hyperlipidemia and enhanced materno- fetal transport may contribute to the fetal macrosomia frequently found in newborns of diabetic women (15).

Concomitant with the presence of an excess of substrates, maternal hyperinsulinaemia enhances fetal lipid synthesis. Insulin receptors may play a role in the increased insulin effects in infants. Several authors have found evidences that a downregulation of the insulin receptors in hyperinsulinaemic fetuses parallels an increased insulin binding. This phenomenon could also explain an enhanced hepatic VLDL levels and hypertriglyceridemia in macrosomic newborns (15, 16).

1.5 Diabetes mellitus

Diabetes mellitus is a chronic metabolic disorder characterized by either absolute or relative insulin deficiency, resulting in increased glucose concentrations. Although glucose intolerance is the common outcome of diabetes mellitus, the pathophysiology is heterogeneous. The two major classifications of diabetes mellitus are type I, formerly referred to as non- insulin or juvenile- onset diabetes, and type II, formerly referred to as non- insulin- dependent or adult- onset diabetes. All forms of diabetes can occur during pregnancy.

1.5.1 Gestational diabetes

Gestational diabetes is defined as carbohydrate intolerance of variable severity with onset or first recognition during the present pregnancy (17). Glucose homeostasis is maintained by the balance between insulin, which reduces glucose

levels by increasing cellular uptake and other hormones such as glucagon and cortisol, which both increase glucose production. During pregnancy the human placenta produces additional cortisol as well as other insulin antagonists such as human placental lactogen, progesterone and human chorionic gonadotropin, all of which tend to increase glucose level. Human placental lactogen blocks insulin receptors and increases in direct linear relation to the length of pregnancy. If the pancreatic β islet cells are unable to produce sufficient insulin to balance this increase, or if there is a maternal resistance, the mother may develop gestational diabetes (18, 19).

The prevalence of GDM varies worldwide and among different racial and ethnic groups. The variability is partly because of the different criteria and screening regimes. The prevalence by NDDG and Carpenter and Coustan criteria, respectively, was 5.0% and 7.4% in Asians, 3.9% and 5.6% in Hispanics, 3.0% and 4.0% in African-Americans, and 2.4% and 3.8% in Whites (18).

The ADA recommend that all pregnant women, who have not been identified with glucose intolerance earlier in pregnancy, be screened with a 50g 1-hour GCT between 24 and 28 weeks of pregnancy. It is seen as a simplified version of the OGTT. It can be performed at anytime of the day and with disregard to previous meal ingestion. A cut- off point is set at 140 mg/dl and identifies approximately 80% of women with GDM, and the yield is further increased to 90% by using a glucose threshold value of 130 mg/dl. However, the diagnosis of GDM is based on an OGTT (20).

For the OGTT, the patient is fasting and receives 100g of glucose after a fasting glucose level is obtained. A blood sample is taken every hour for 3 hours. Women with clinical characteristics consistent with a high risk of GDM (marked obesity, previous GDM, glycosuria, macrosomia or polyhydramios, or a strong family history of diabetes) should undergo glucose testing as soon as feasible. If they are found not to have GDM at that initial screening, they should be retested between 24 and 28 weeks of gestation.
Two or more of the following values must be met or exceeded for a positive diagnosis of GDM (20).

Fasting blood glucose level ≥ 95 mg/dl
1 hour blood glucose level ≥ 180 mg/dl
2 hour blood glucose level ≥ 155 mg/dl
3 hour blood glucose level ≥ 140 mg/dl

Most women have no clinical features, but are diagnosed after screening. GDM is associated with an increased risk of macrosomia and pre-eclampsia.

The reason for a medical management is to lower the glucose level to a normoglycemic (fasting plasma glucose = ≤105 mg/dl) one to prevent diabetic complications. The overall goal of intervention is to prevent perinatal morbidity and mortality by normalizing the level of glycemia and other metabolites like lipids to the levels of nondiabetic pregnant women. Nutritional counseling is the mainstay of therapy for the gestational diabetic women. If diet is not successful in maintaining relative euglycemia, then insulin therapy is recommended (20).

Most of time, gestational diabetes is a short- term condition. Blood glucose levels go back to normal once the pregnancy ends. However, mothers have an increased risk of developing diabetes mellitus in future. If they required insulin for their pregnancy, there is a 50% risk of diabetes within 5 years. If dietary control has been sufficient, a 60% risk of developing diabetes mellitus within 10- 15 years still persists (21). Also children of women with GDM have an increased risk for childhood and obesity and an increased risk of glucose intolerance and type 2 diabetes later in live (22). This risk relates to increased maternal glucose values (23).

1.5.2 Insulin dependent diabetes mellitus

Insulin dependent diabetes mellitus is characterized by an abrupt onset at a young age and absolute insulinopenia with live- long requirements for insulin replacement. Patients with diabetes mellitus may have a genetic predisposition for antibodies directed against their pancreatic β islet cells and so they are completely dependent on exogenous insulin. Additionally intensive insulin therapy is used in pregnant women with type 1 diabetes to decrease the risk for spontaneous

abortion and congenital anomalies in early gestation. It is associated with a variety of pregnancy complications like an increasing risk of pre- eclampsia, infections, worsening diabetic retinopathy and diabetic nephropathy. Insulin requirements are usually doubled during the pregnancy. Because of a difficult glycaemic control increased hypoglycaemic episodes are more common in pregnancy.

For the fetus the risk of maternal IDDM are miscarriage, fetal abnormality, intrauterine growth restriction, macrosomia, polyhydramnios, sudden intrauterine death increased neonatal mortality. Specific congenital abnormalities include cardiac disease, neural tube defects and sacral agenesis (24).

A pre- pregnancy consultation is crucial for diabetic mothers to reduce maternal and fetal risks. The number of insulin injections may be increased and a different combination of short- and longer- acting insulin used to maintain the blood glucose.

A detailed scan is needed in the first and second trimester in view of the increased risks of mother and fetus.

The mode of delivery depends on previous obstetrics history, estimated fetal weight and predicted risk of shoulder distocia. Most diabetic women are delivered by caesarean section (20).

The insulin dose is dropped immediately after delivery to the pre- pregnancy regime, as insulin requirements return to the non- pregnant state within 24 hours.

2 Methods

This chapter specifies the structure and used methods of literature search for this thesis.

The objective of this literature work is to describe and compare studies where changes in serum lipid- lipoprotein and apolipoprotein concentrations during and after pregnancy in control and in diabetic women as well as in newborns of normal and diabetic mothers were analyzed. Lipid profiles of nondiabetic women are compared with levels of women with gestational diabetes mellitus and women with Type I diabetes mellitus. Newborns of nondiabetic mothers and newborns of diabetic mothers are compared.
Another goal of this thesis is to extract differences between the studies in terms of study populations and analytical methods, which may account for the confusing interpretations between reviews and literature. Parameters that play role in alterations in maternal and fetal lipoprotein profile in normal and diabetic pregnancy are worked out in this paper.

First of all a structured literature search in one of the medical scientific database www.pubmed.com was conducted. Limitations: Only German- and English-speaking literature from 1974 to 2008 were taken out of the database. Literature researches in databases like in www.pubmed.com are conducted with key words respectively with names of international known scientists. Following Key words were used in following combinations:

- Mother, pregnancy, lipoprotein, total cholesterol, LDL, HDL
- Mother, placenta, lipoprotein, total cholesterol, LDL, HDL
- Fetal, pregnancy, lipoprotein, LDL, HDL
- Fetal, placenta, lipoprotein, LDL, HDL
- Lipoprotein profile changes, pregnancy, GDM
- Lipoprotein profile changes, pregnancy, IDDM
- GDM, mother, pregnancy, lipoprotein
- GDM, fetal, pregnancy, lipoprotein
- Placenta, lipoprotein, LDL, HDL

- Diabetes, GDM, lipoprotein, fetal
- Lipid metabolism, pregnancy
- Lipid metabolism, fetus and newborn
- Lipid metabolism, diabetic pregnancy

Additional literature were taken out from books of the library from the Medical University Graz and cited in the text.

The huge number of publications was finally selected by relevant subject area. Preferences were given to studies, which revealed comparable lipoprotein and apolipoprotein concentrations in tables and/or figures. Furthermore, there was a bias towards literature, which shows differences between lipoprotein and apolipoprotein levels in nondiabetic and diabetic mothers and newborns of nondiabetic and diabetic mothers.

At the beginning of this work, available literature is researched and arranged according to the categories stated above. To make an overview over all studies where lipoprotein and apolipoprotein concentrations were measured and to amplify differences and contradictions, all values were summarized shown in distinct figures. Based on these figures and additional information out of the papers, results were analyzed, compared and discussed.

A systemic research of following enzymes revealed no hits: apolipoprotein E, non-esterified fatty acids, HDL- cholesterol ester, different lipases and enzymes. So they where not discussed.

Table 2: Overview of all analyzed studies

Maternal side			**TG (mmol/l)**	**LDL- C (mmol/l)**	**HDL-C (mmol/l)**	**TC (mmol/l)**	**apoB (mmol/l)**	**apo A1 (mmol/l)**
Longitudinal study on lipoprotein profile, high density lipoprotein subclass, and postheparin lipase during gestation in woman **1996 (1st trimester)**	Alvarez et al	**AGA**	0,69	2,31	1,76	4,41		
		GDM						
		IDDM						
Longitudinal study on lipoprotein profile, high density lipoprotein subclass, and postheparin lipase during gestation in woman **1996 (3rd trimester)**	Alvarez et al	**AGA**	2,13	3,96	1,84	6,57		
		GDM						
		IDDM						
Lipid metabolism in pregnancy. III. altered lipid composition in intermediate, very low, low, and high-density lipoprotein fractions; **1957 (gestational age: 34-42 weeks)**	Warth et al	**AGA**	2,49	2,54	1,57	5,51		
		GDM						
		IDDM						
Serum lipid, lipoprotein and apolipoprotein changes in gestational diabetes mellitus: a cross-sectional and prospective study **1996 (gestational age: 30-31 weeks)**	Koukkou et al	**AGA**	2,1	4,01	1,72	6,71		
		GDM	2,92	3,08	1,71	6,23		
		IDDM						
Serum lipid, lipoprotein and apolipoprotein changes in gestational diabetes mellitus: a cross-sectional and prospective study **1996 (gestational age: 30-31 weeks)**	Koukkou et al	**AGA**	0,94	2,69	1,22	4,43		
		GDM	1,16	2,72	1,3	4,64		
		IDDM						

Maternal side			TG (mmol/l)	LDL- C (mmol/l)	HDL-C (mmol/l)	TC (mmol/l)	apoB (mmol/l)	apo A1 (mmol/l)
Maternal and cord plasma lipid and lipoprotein concentration s in woman with and without gestational diabetes mellitus **1998 (gestational age: 37- 38 weeks)**	Couch et al	**AGA**	2,03	2,62	1,81	6,02		
		GDM	2,69	2,49	1,83	5,73		
		IDDM						
Elevated lipoprotein lipids and gestational hormones in woman with diet-treated gestational diabetes mellitus compared to healthy pregnant controls **1998 (gestational age: 26-30 weeks)**	Couch et al	**AGA**	1,55	2,35	1,83	5,58		
		GDM	2,07	2,12	3,65	5,13		
		IDDM						
Elevated lipoprotein lipids and gestational hormones in woman with diet-treated gestational diabetes mellitus compared to healthy pregnant controls **1998 (gestational age: 33-34 weeks)**	Couch et al	**AGA**	1,9	2,33	1,81	5,73		
		GDM	2,66	2,01	3,61	5,32		
		IDDM						
Elevated lipoprotein lipids and gestational hormones in woman with diet-treated gestational diabetes mellitus compared to healthy pregnant controls **1998 (gestational age: 37-38 weeks)**	Couch et al	**AGA**	1,98	2,56	1,83	5,9		
		GDM	2,77	2,41	3,61	5,58		
		IDDM						
Postpartum oral glucose tolerance tests in mothers of macrosomic infants: inadequacy of current antenatal test criteria in detecting prediabetic state **1998 (postpartum)**	Bukulmez et al	**AGA**	1,91	2,79	1,93	5,48		
		GDM	2,61	3,27	1,66	6,81		
		IDDM						
Maternal triglyceride levels and newborn weight in pregnant woman with normal glucose tolerance **2003 (3rd trimester)**	Di Cianni et al	**AGA**	1,99	4,01	1,68	6,34		
		GDM	2,47	3,9	1,6	6,59		
		IDDM						

Maternal side			**TG (mmol/l)**	**LDL- C (mmol/l)**	**HDL-C (mmol/l)**	**TC (mmol/l)**	**apoB (mmol/l)**	**apo A1 (mmol/l)**
Impact of gestational diabetes on lipid profiling and indices of oxidative stress in maternal and cord plasma **2004 (3rd trimester)**	Sobki et al	**AGA**	2,93	3,71	1,71	6,73		
		GDM	3,47	3,64	1,73	6,44		
		IDDM						
Metabolic disorders in patients with recent gestational diabetes mellitus **2005 (postpartum)**	Eroglu et al	**AGA**	0,7		1,33	3,9		
		GDM	1,03		1,4	4,9		
		IDDM						
Association of gestational diabetes mellitus and low -density lipoprotein (LDL) particle size **2006 (gestational age: 37-39 weeks)**	Qiu et al	**AGA**	2,04	2,57	1,45	4,97		
		GDM	2,55	2,27	1,27	4,71		
		IDDM						
Pregnancy- associated hypertriglyceridemia in normal and diabetic woman - differences in insulin- dependent, non- insulin- dependent, and gestational diabetes **1982 (gestational age: 25-27)**	Hollingsworth et al	**AGA**	2,12			6,5		
		GDM	3,27			6,23		
		IDDM	1,75			5,95		
Pregnancy- associated hypertriglyceridemia in normal and diabetic woman - differences in insulin- dependent, non- insulin- dependent, and gestational diabetes **1982 (gestational age: 34-37)**	Hollingsworth et al	**AGA**	2,56			6,7		
		GDM	3,1			5,8		
		IDDM	2,74			6,7		
Pregnancy- associated hypertriglyceridemia in normal and diabetic woman - differences in insulin- dependent, non- insulin- dependent, and gestational diabetes **1982 (postpartum)**	Hollingsworth et al	**AGA**	0,94			5,27		
		GDM	1,69			5,38		
		IDDM	1,13			4,76		

Maternal side			TG (mmol/l)	LDL- C (mmol/l)	HDL-C (mmol/l)	TC (mmol/l)	apoB (mmol/l)	apo A1 (mmol/l)
Relationship of lipoprotein lipids to mild fasting hyperglycemia and diabetes in pregnancy **1981 (gestational age: 32 weeks)**	Knopp et al	**AGA**	2,03		1,81			
		GDM						
		IDDM	1,58		1,69			
Relationship of lipoprotein lipids to mild fasting hyperglycemia and diabetes in pregnancy **1981 (gestational age: 36 weeks)**	Knopp et al	**AGA**	2,14		1,68			
		GDM						
		IDDM	1,99		1,79			
Fetal and maternal lipoprotein metabolism in human pregnancy complicated by type I diabetes mellitus **1998 (gestational age: 37-38 weeks)**	Kilby et al	**AGA**	3,01	3,76	0,96	7,48		
		GDM						
		IDDM	2,55	2,97	1,14	7,08		
Changes in serum lipid and lipoprotein concentrations and compositions at birth and after 1 month of life in macrosomic snfants of insulin-dependant diabetic mothers **1998 (3rd trimester)**	Merzouk et al	**AGA**						
		GDM						
		IDDM						
Maternal and fetal lipid serum lipid and lipoprotein concentration and composition in type 1 diabetic pregnancy: relationship with maternal glicemic control **1999 (3rd trimester)**	Merzouk et al	**AGA**	2,01	4,64	1,8	7,04		
		GDM						
		IDDM	3,62	5,22	1,43	7,35		

Fetal side			TG (mmol/l)	LDL- C (mmol/l)	HDL-C (mmol/l)	TC (mmol/l)	apoB (mmol/l)	apo A1 (mmol/l)
Maternal and cord plasma lipid and lipoprotein concentration s in woman with and without gestational diabetes mellitus **1998**	Couch et al	**AGA**						
		GDM	0,49		0,57	1,42		
		IDDM	0,42		0,55	1,39		
Postpartum oral glucose tolerance tests in mothers of macrosomic infants: inadequacy of current antenatal test criteria in detecting prediabetic state **1998**	Bukulmez et al	**AGA**	0,43	0,83	1,49	2,31		
		GDM	0,59	0,97	1,13	2,52		
		IDDM						
Impact of gestational diabetes on lipid profiling and indices of oxidative stress in maternal and cord plasma **2004**	Sobki et al	**AGA**	0,64	1,97	0,72	2,03		
		GDM	0,31	0,86	0,68	1,51		
		IDDM						
Serum lipid and lipoprotein composition in infants of diabetic mothers **1999**	Akisü et al	**AGA**	0,42	1,13	1,05	2,55	0,69	0,64
		GDM	0,46	1,5	0,95	2,78		
		IDDM	0,5	1,6	0,9	2,7	0,58	0,47
Lipoprotein (a) and lipid profile in neonates from mothers with three different types of diabetes mellitus **2003**	Abou Ghalia et al	**AGA**	0,46	0,61	0,75	1,7	0,27	0,14
		GDM	0,38	0,81	0,9	1,9		
		IDDM	0,62	0,38	0,88	1,6	0,62	0,27
Fetal and maternal lipoprotein metabolism in human pregnancy complicated by type I diabetes mellitus **1998**	Kilby et al	**AGA**	0,29	0,59	0,66		0,69	0,35
		GDM						
		IDDM	1,06	0,76	0,83		1,43	0,68

Fetal side			TG (mmol/l)	LDL- C (mmol/l)	HDL-C (mmol/l)	TC (mmol/l)	apoB (mmol/l)	apo A1 (mmol/l)
Changes in serum lipid and lipoprotein concentrations and compositions at birth and after 1 month of life in macrosomic infants of insulin-dependant diabetic mothers **1998**	Merzouk et al	**AGA**	0.58	0,44	1,06	1,74		
		GDM						
		IDDM	1,44	0.68	1	2,18		
Maternal and fetal lipid serum lipid and lipoprotein concentration and composition in type 1 diabetic pregnancy: relationship with maternal glycemic control **1999**	Merzouk et al	**AGA**	0,52	0,59	0,99	1,51	0,68	
		GDM						
		IDDM	0,54	0,6	1,01	1,73	0,84	
IGF-1 and leptin associate with fetal HDL cholesterol at birth examination in offspring of mothers with type 1 diabetes **2007 (female sex)**	Nelson et al	**AGA**	0,46	0,75	0,65	1,72		
		GDM						
		IDDM	0,44	0,9	0,7	1,81		
IGF-1 and leptin associate with fetal HDL cholesterol at birth examination in offspring of mothers with type 1 diabetes **2007 (male sex)**	Nelson et al	**AGA**	0,44	0,77	0,74	1,74		
		GDM						
		IDDM	0,38	0,75	0,53	1,49		
Cord blood serum in newborns of diabetic mothers **1982** (**male sex)**	Fordyce et al	**AGA**	0,54	0,38	1,14	0,54		
		GDM						
		IDDM	0,38	0,53	1,13	0,38		
Cord blood serum in newborns of diabetic mothers **1982 (female sex**)	Fordyce et al	**AGA**	0,44	0,66	1,09	0,44		
		GDM						
		IDDM	0,42	0,76	0,83	0,42		

3 Results and Discussions

3.1 Maternal lipid and lipoprotein profile

Figure 6: Lipid concentration in **non- pregnant** women

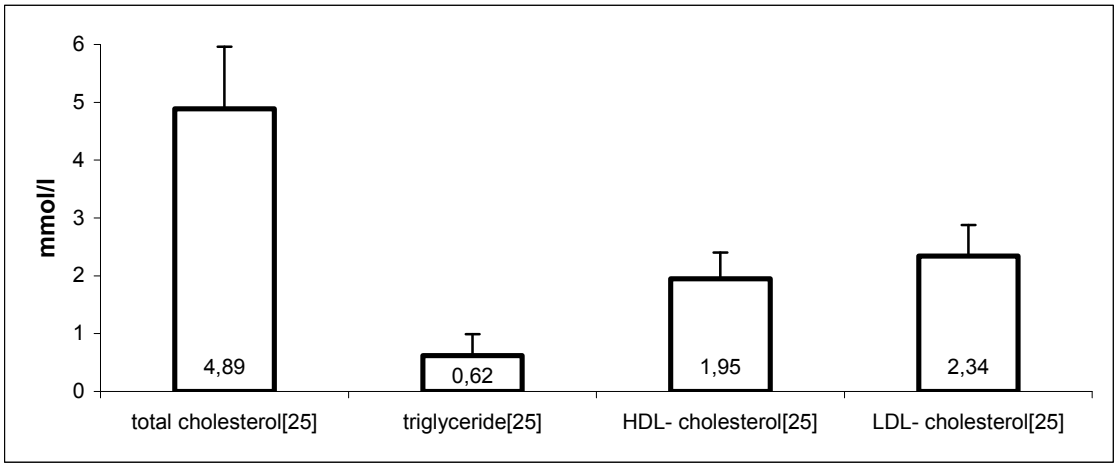
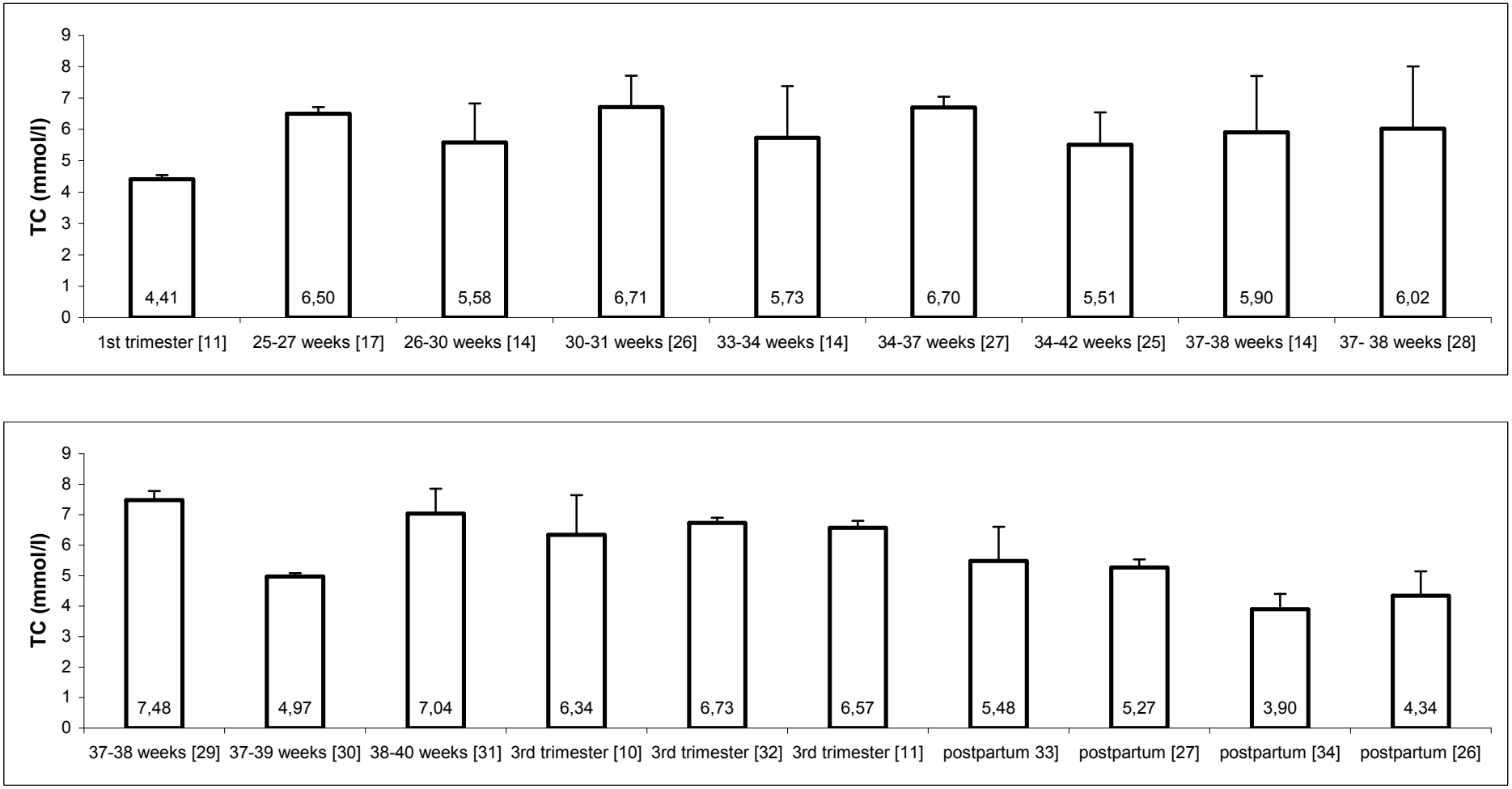


Figure 6 demonstrates lipid concentration in non pregnant women. Warth et al (25) studied ten non- pregnant, healthy and premenopausal women. None of them were taking oral contraceptives. None were grossly obese or known to be diabetic. This group of non- pregnant controls is used in the paper for comparison with healthy and diabetic pregnant subjects.

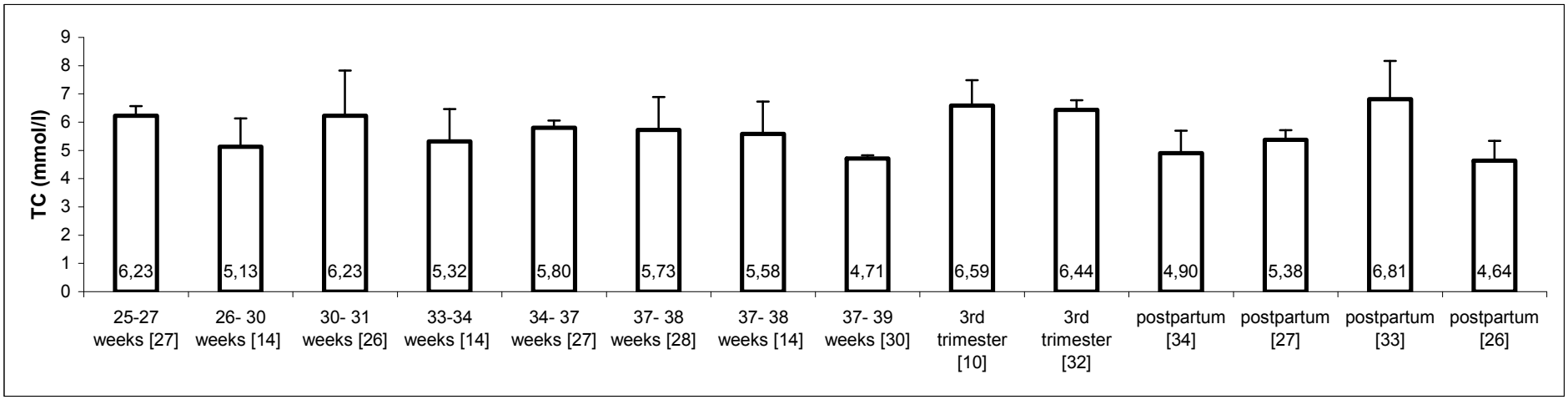
3.1.1 Total cholesterol concentrations

Figure 7 A: Maternal total cholesterol levels in controls



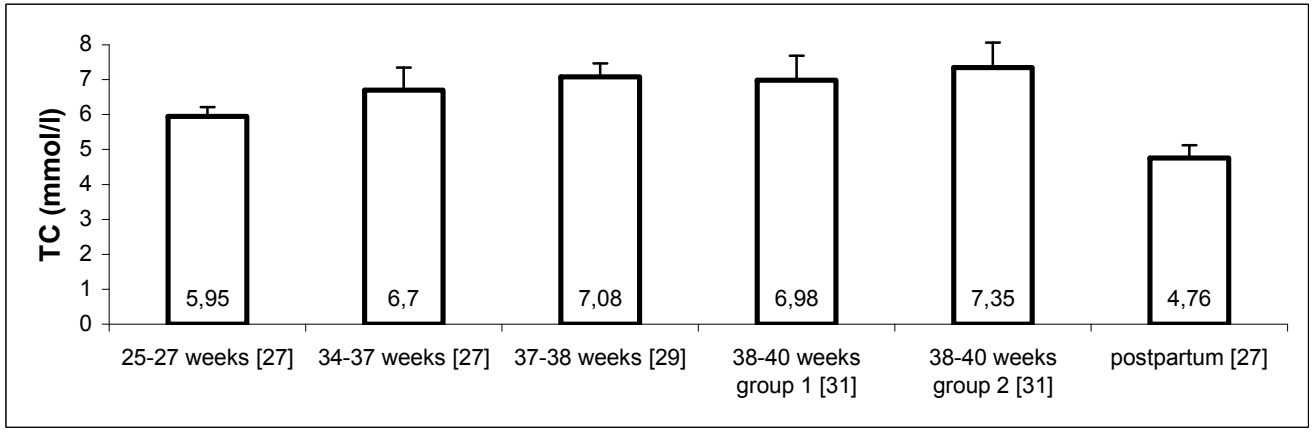
Mean maternal total- cholesterol levels in controls including all studies = **5,85 ± 0,98 mmol/l**

Figure 7 B: Maternal total cholesterol levels in GDM



Mean maternal total- cholesterol levels in GDM including all studies = **5,68 ± 0,71 mmol/l**

Figure 7 C: Maternal total cholesterol levels in IDDM



Mean maternal total- cholesterol levels in IDDM including all studies = **6,47 ± 0,96 mmol/l**

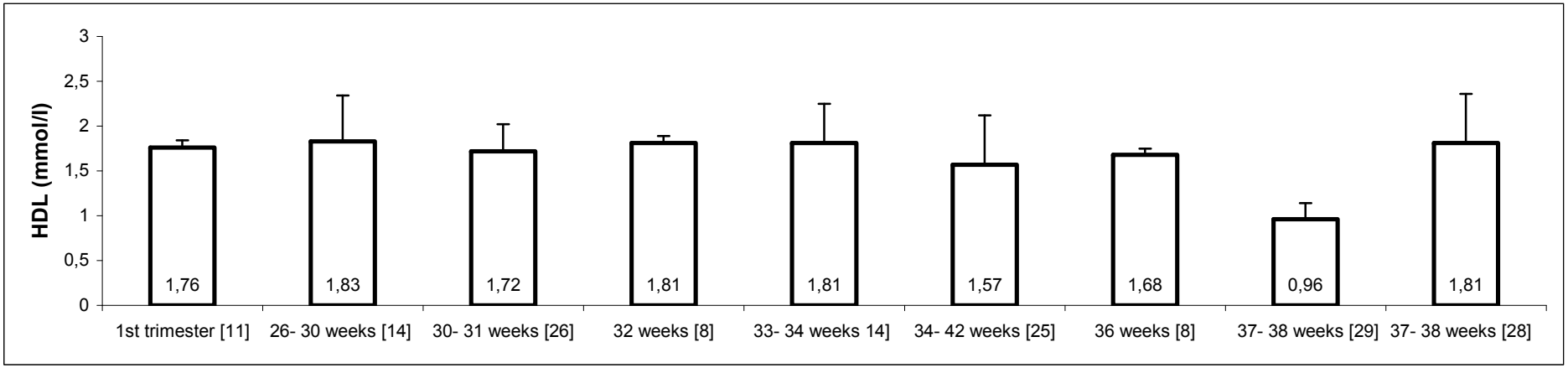
Figures 7 A summarizes results for total cholesterol concentrations [mmol/l] in control pregnancies from the first to the third trimester and postpartum. All studies revealed a continual elevation in total cholesterol levels from the first to the third trimester of pregnancy. Postpartum an expected decrease in total cholesterol concentration in relation to pregnant status can be consistently observed, except in the study of Hollingsworth (27). In this study significantly higher mean maternal postpartal total cholesterol concentrations were measured. This obvious discrepance can be explained by the different timepoint of sample analysis. In Hollingsworth's study the sample measurements were done three month postpartum whereas in Eroglu`s (34) study the sample evaluation varied from ten to fifteen months after delivery. These results led to the assumption that enzymatically determination of cholesterol concentrations depends on the time point of analyses. Mode of sample storage, frequently thawing and frezzing of the samples and different analytical methods are possible factors, which can influence the results.

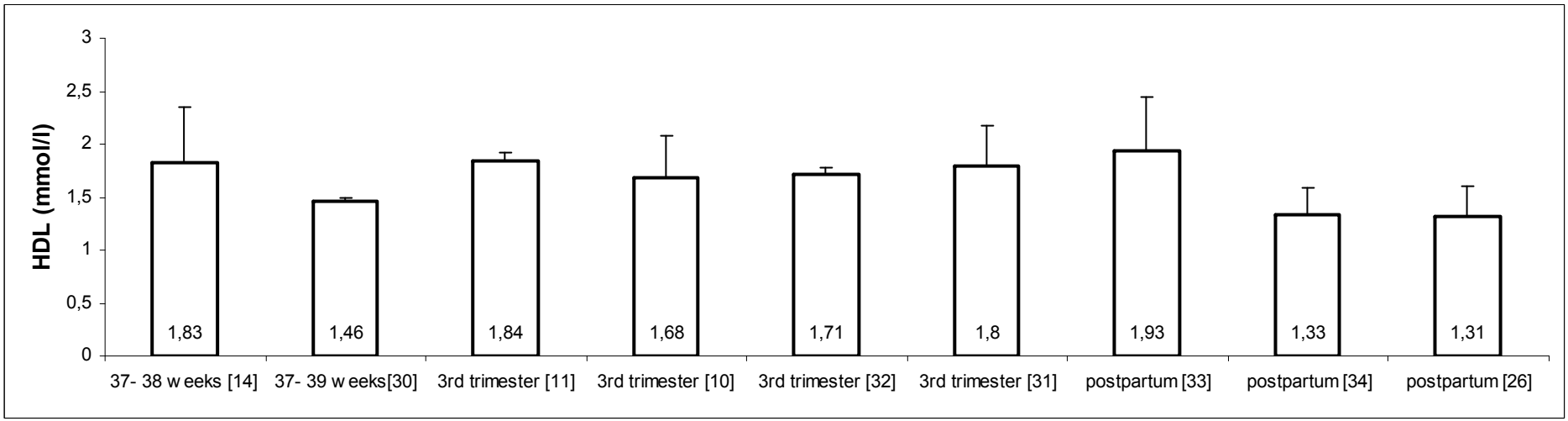
Postpartal GDM cholesterol concentration in the study of Bukulmez et al (33) was significantly higher in GDM than in the healthy control group. Bukulmez et al (33) measured a 1.3 fold higher maternal total cholesterol level in GDM compared to controls. Obviously, the diet treatment of the GDM mothers, described in this study, modulates cholesterol levels over the time of pregnancy.

In all three studies (27, 29,31), which are compared in Figure 7 C a continual not very marked rise of total cholesterol levels during pregnancy in type I patients was detected. Interestingly matched controls as well as compared to other studies the cholesterol values are in general lower.

3.1.2 HDL- cholesterol concentrations

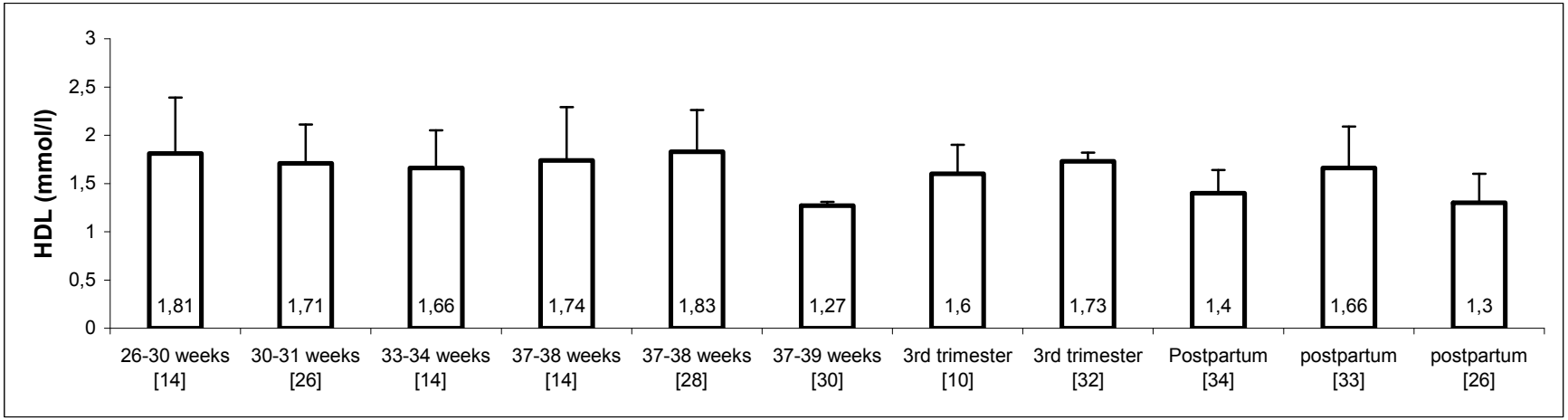
Figure 8 A: Maternal HDL- cholesterol levels in controls





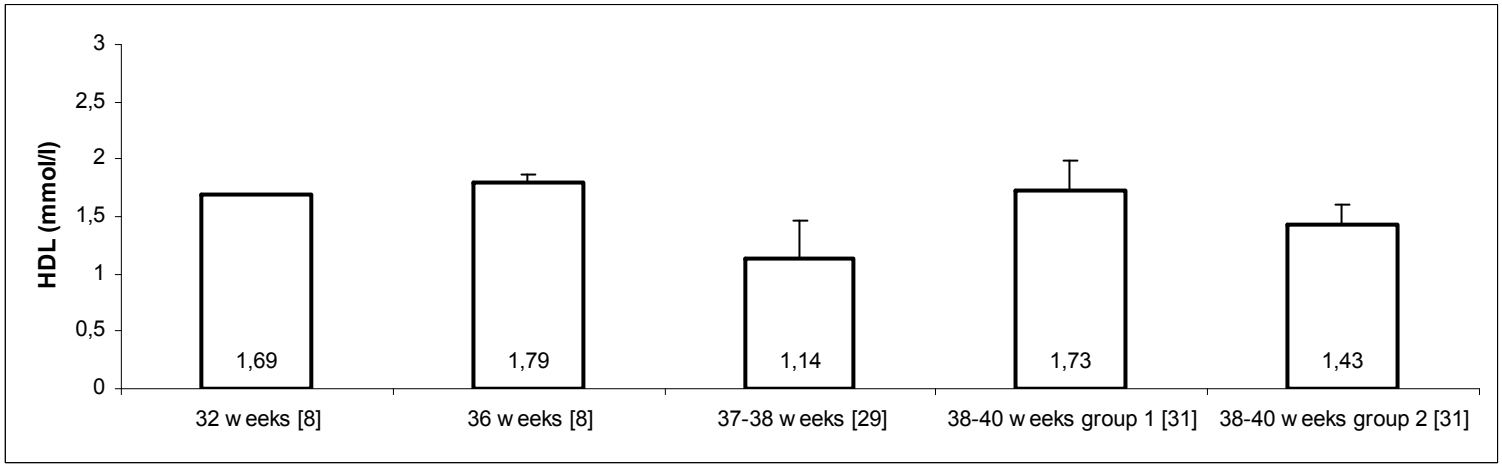
Mean maternal HDL- cholesterol levels in controls including all studies = **1,66 ± 0,25 mmol/l**

Figure 8 B: Maternal HDL- cholesterol levels in GDM



Mean maternal HDL- cholesterol levels in GDM including all studies = **1,49 ± 0,29 mmol/l**

Figure 8 C: Maternal HDL- cholesterol levels in IDDM

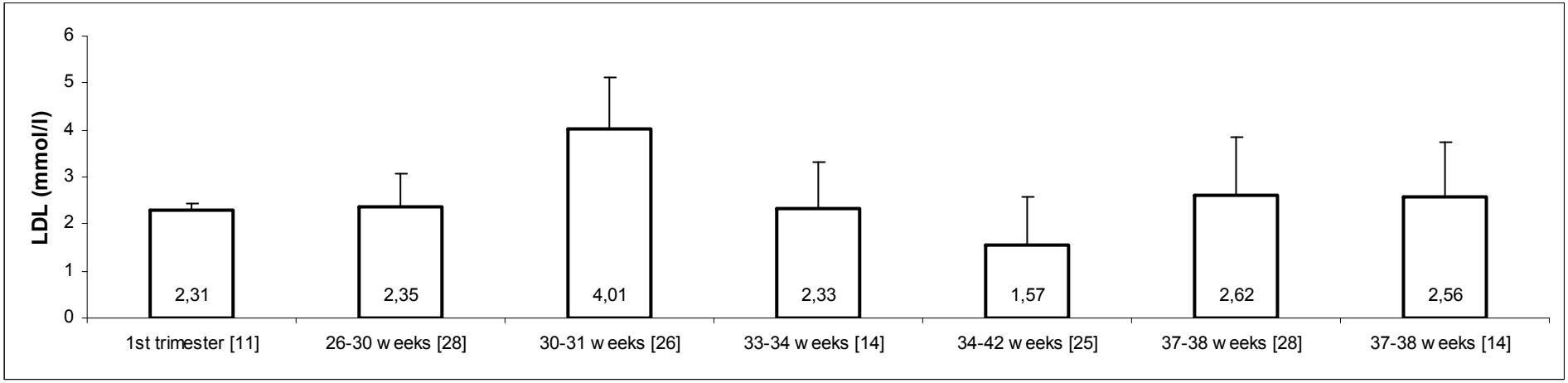


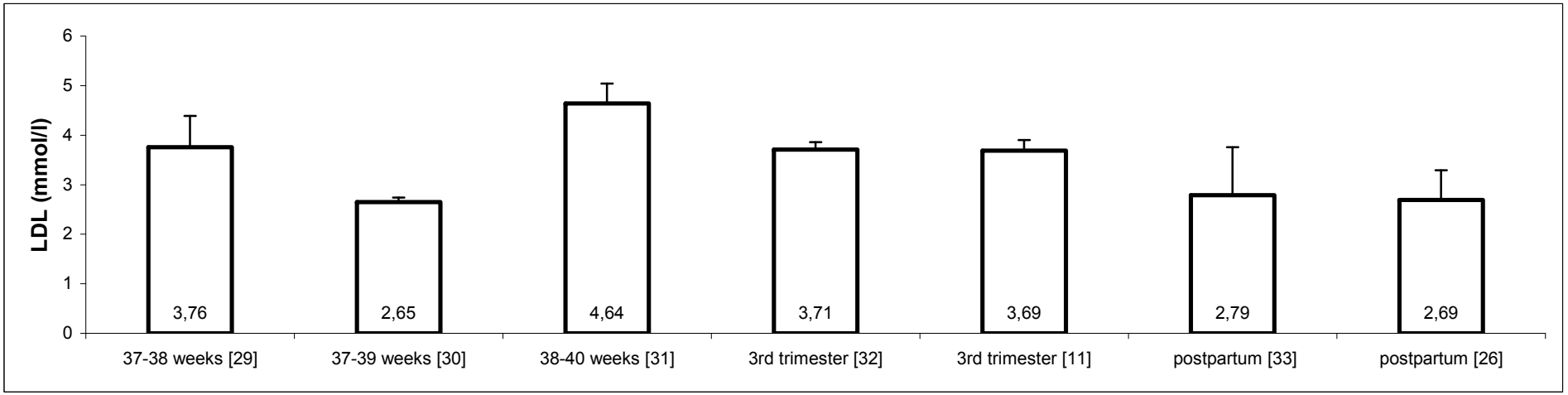
Mean maternal HDL- cholesterol levels in IDDM including all studies = **1,56 ± 0,27 mmol/l**

Figure 8 describes maternal HDL- cholesterol alterations in pregnant women with gestational diabetes, with type 1 diabetes mellitus and healthy pregnant women. Women were studied longitudinally during the three trimesters of gestation and at postpartum. No meaningful modification in HDL- cholesterol during gestation is found in nondiabetic or in diabetic pregnancy.

3.1.3 LDL- cholesterol concentrations

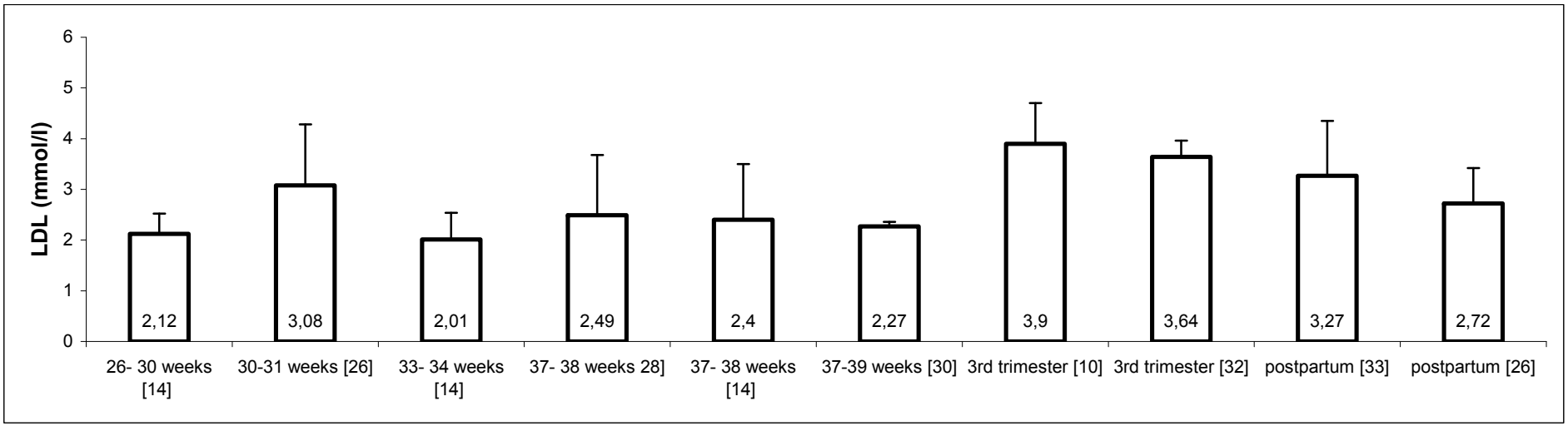
Figure 9 A: Maternal LDL- cholesterol levels in controls





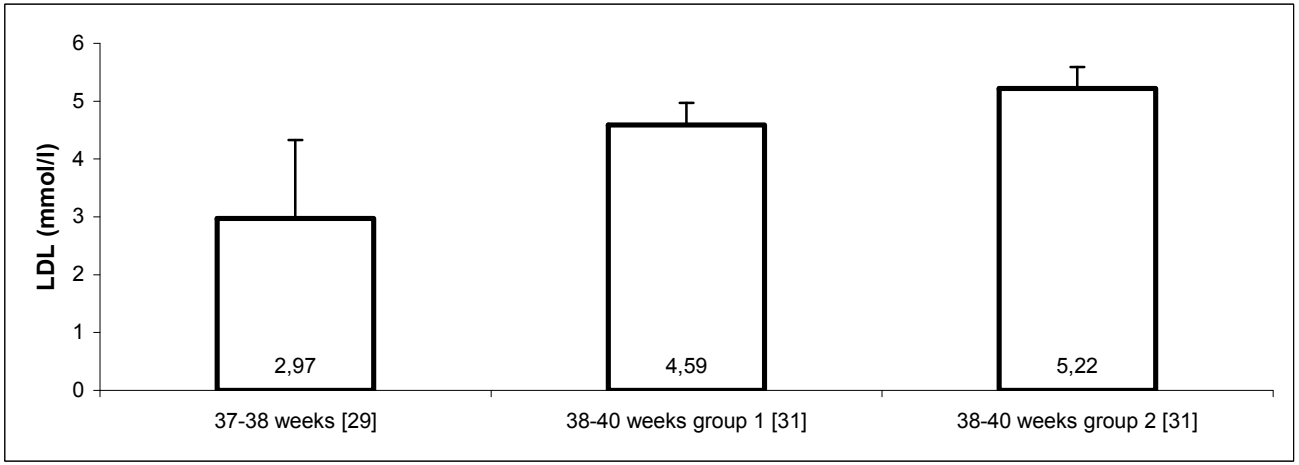
Mean maternal LDL- cholesterol levels in controls including all studies = **3,00 ± 0,82 mmol/l**

Figure 9 B: Maternal LDL- cholesterol levels in GDM



Mean maternal LDL- cholesterol levels in GDM including all studies = **2,79 ± 0,65 mmol/l**

Figure 9 C: Maternal LDL- cholesterol levels in IDDM



Mean maternal LDL- cholesterol levels in IDDM including all studies = **4,26 ± 1,16 mmol/l**

Figure 9 A demonstrates alterations in maternal LDL-cholesterol concentrations during gestation and postpartum of different published studies. In general it is noticeable that with increasing gestational age the LDL-cholesterol levels increase in the maternal circulation.

In this context three studies are needed to be discussed regarding remarkable cholesterol levels. Beside Merzouk´s (31) study, in Koukkou´s (26) study higher maternal LDL-concentrations were detected compared to the other studies. This discrepance can be explained by the different method of analytical measurement. After an enzymatic analysis on a DAX-96 analyser (Bayer Diagnostics, Basingstoke, UK) of total serum cholesterol and triglyceride and a HDL- measurement after dextran sulphate/ magnesium chloride precipitation of Apo B containing lipoproteins (Bayer Diagnostics) they recalculated the LDL cholesterol concentrations by the Friedewald method. This method has potential limitations. Changes in lipoprotein cholesterol concentrations are the result of compositional changes in protein and lipid proportions and therefore each lipoprotein fraction should be measured directly. The most appropriate method to analyze human serum or plasma is the compartmentalisation by ultracentrifugation and afterwards to measure the chemical composition or size of the fractions by using electrophoresis (26). For example in the study of Warth et al (25) who used a stepwise sequential ultracentrifugation found twice lower LDL-cholesterol concentrations compared to Koukkou´s (26) study in the same control group. It is now widely accepted that with the method of plasma ultracentrifugation the highest separation performance into different lipoprotein fractions can be achieved (35). Therefore, the exceeding LDL-cholesterol levels in Koukkou´s (26) study may a result from indirect analysis of the maternal lipoproteins.

Also in the study of Merzouk et al (31) (Figure 9 A) a significantly higher maternal LDL-cholesterol levels is measured. It can be seen a 1.5- fold difference from the mean value of 3.00 ± 0.82 mmol/l. It is known from other investigations that age, race and prepregnancy body-mass index (BMI) are cofactors, which effect plasma lipid concentrations (26).Merzouk et al (31) recruited pregnant woman exclusively from Algeria. Furthermore Koukkou et al (36) found differences in serum lipid-, lipoprotein- and apolipoprotein concentrations in Caucasian compared to African/Caribbean pregnant women. So we cannot exclude the possibility that the different ethnic origin of pregnant women in the study of Merzouk et al (31) causes a higher LDL-cholesterol level compared to others.

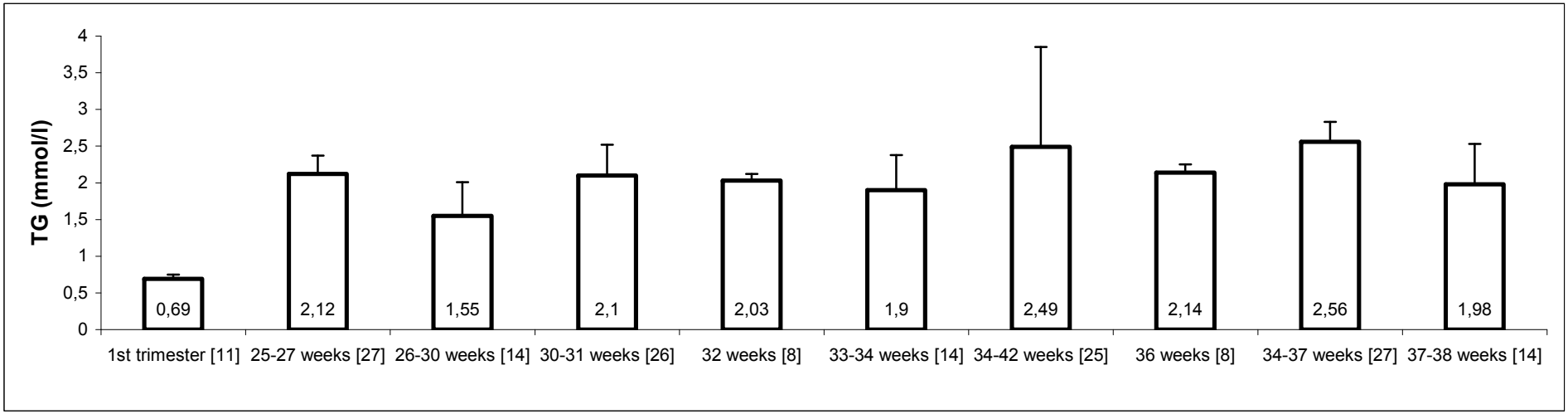
Figure 9 B gives an overview of studies where maternal LDL-cholesterol levels in GDM were measured. Couch et al (14) studied 25 women with GDM and compared LDL levels with 25 controls at 26-30 weeks, at 33-34 weeks and at 37-38 weeks of pregnancy. Generally, 1.5- fold lower LDL cholesterol concentrations in the group of women with GDM compared to controls were quantified. These results are in agreement with those of Qiu et al (30) and Sobki et al (32) and others who also reported lower LDL cholesterol levels in their GDM population compared with controls.

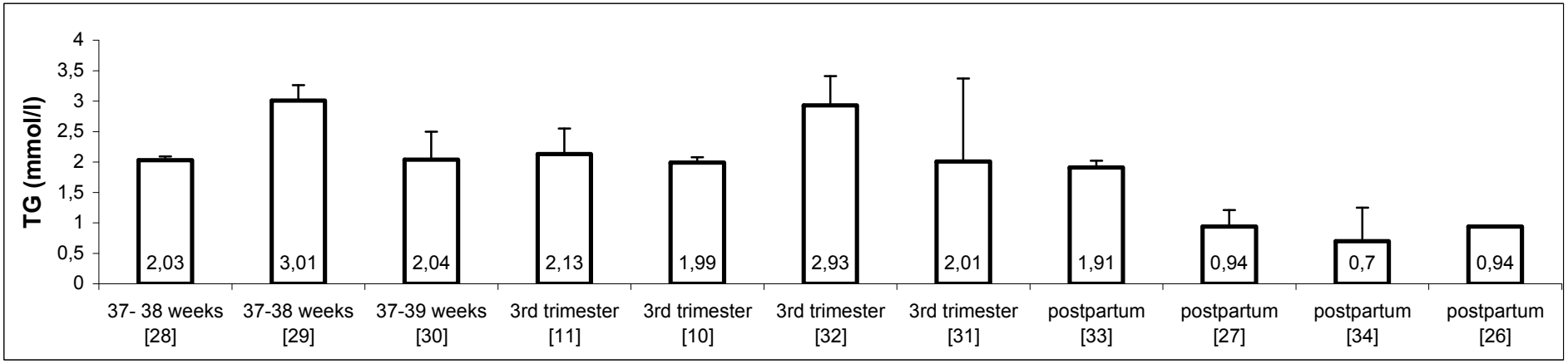
However, Bukulmez et al (33) found 1.7- fold higher LDL- cholesterol concentrations in GDM patients in the first 48 h after delivery compared to controls. To my opinion this study has several limitations. First of all, analysis of the relatively small sample size (n= 10) may have failed to detect significant differences in lipid concentrations after pregnancy. Bukulmez et al (33) studied only 10 GDM cases and compared them with 50 control subjects. Secondly, only total triglyceride and total cholesterol levels were analysed by enzymatically. HDL cholesterol was measured after Mg2+/ dextran sulphate precipitation. Afterwards LDL cholesterol concentration was recalculated by the Friedewald equation. This way of measurement is not state of the art for comparing lipoprotein concentrations.

Figure 9 C compares studies of maternal LDL-cholesterol concentrations in pregnant women with type I diabetes mellitus. In the study of Merzouk et al (31) LDL-cholesterol levels in diabetic mothers are elevated. Merzouk et al (31) measured 1.7-fold higher LDL- cholesterol levels than Kilby et al (29) measured. In particular the authors of the study of Merzouk et al (31) studied two groups of diabetic mothers. All women (n= 40), Algerian were treated with insulin during pregnancy, but 20 were poorly controlled. In these women with poorly controlled diabetes, obstetric and diabetic management was inadequate, since many lived considerable distances from any medical center. In addition, these women did not use home capillary blood glucose monitoring and the insulin regimens were not regularly adjusted. So it is surprising that no significant difference in LDL- cholesterol levels were detected between women with well- controlled diabetes and women with poorly controlled diabetes.

3.1.4 Triglyceride concentrations

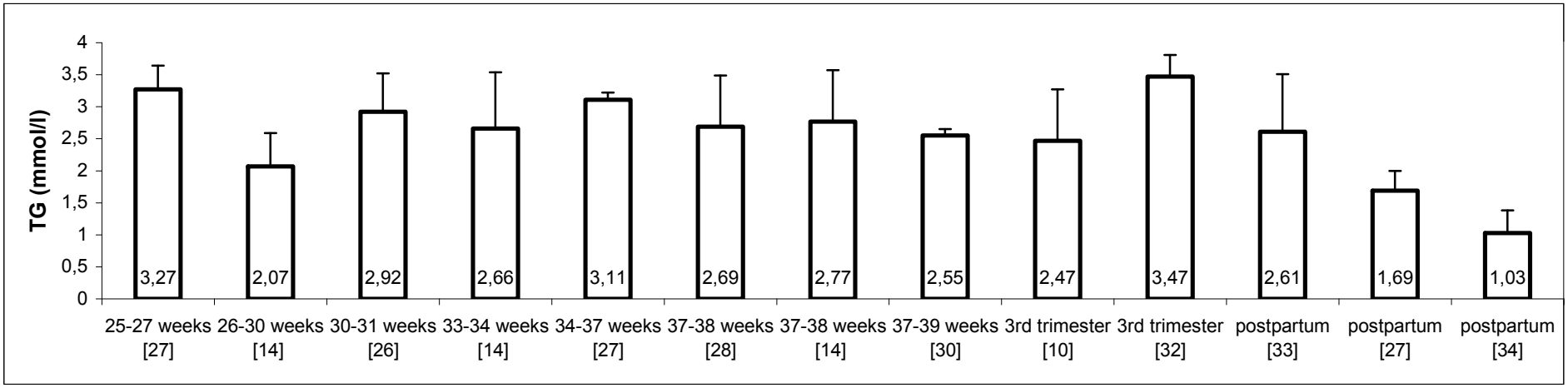
Figure 10 A: Maternal triglyceride levels in controls





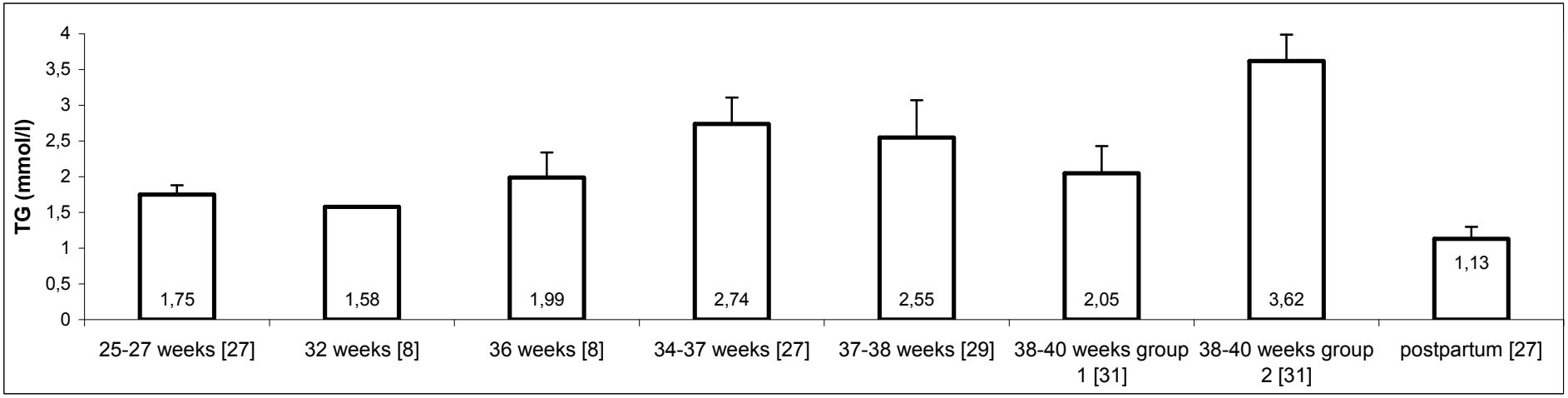
Mean maternal triglyceride levels in controls including all studies = **1,89 ± 0,61 mmol/l**

Figure 10 B: Maternal triglyceride levels in GDM



Mean maternal triglyceride levels in GDM including all studies = **2,56 ± 0,66 mmol/l**

Figure 10 C: Maternal triglyceride levels in IDDM



Mean maternal triglyceride levels in IDDM including all studies = **2,18 ± 0,78 mmol/l**

In Figure 10 A results of triglyceride concentrations from the first to the third trimester and postpartum in healthy pregnant women are compared. All studies observed an increase in triglyceride concentrations from second to third trimester. All studies found similar comparable triglyceride concentrations in the maternal circulation.
The study of Bukulmez et al (33) revealed 2.7- fold higher postpartum triglyceride levels compared to Eroglu et al (34). In opposition to Bukulmez et al (33) which tested there patients within 48 hours after delivery Eroglu et al (34) made there measurements from 10 to 15 month after delivery.

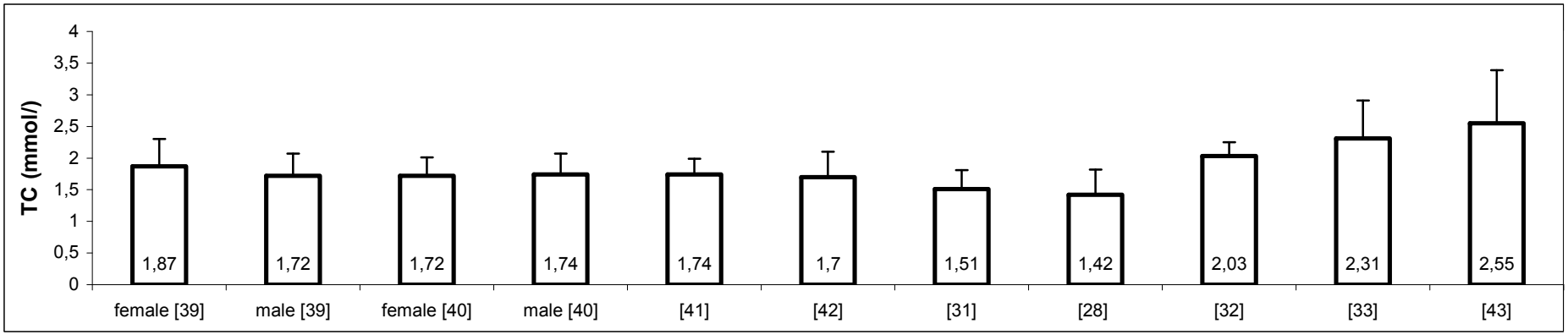
Patients with GDM had significantly elevated triglyceride concentration at all times of pregnancy compared to controls (Figure 10 B). They show a 1.4- fold higher triglyceride level compared to the mean value of 1.89 ± 0.61 mmol/l in control patient group.
In normal pregnancy, in late gestation, cellular resistance to insulin increases, paralleling an increase in adipose tissue lipolyses (37). These physiologic changes result in increased plasma FFA and consequently, in increased hepatic TG synthesis and secretion (37). Additionally, insulin resistance during pregnancy has been shown to produce a decline in lipoprotein lipase (LPL) activity and may contribute to decreased peripheral catabolism of VLDL TG (38). In individuals with these metabolic disorders, a reduced or ineffective concentration of circulating insulin results in an inability of the body to use glucose as an energy substrate. The increased plasma and lipoprotein TG concentrations in GDM as compared to the control group lend support to this concept.It is of interest that all studied pregnant woman with GDM were older and had a higher prepregnancy BMI (kg/m2) compared to controls (14).

Triglyceride concentrations in IDDM patients are shown in Figure 10 C. As we can see levels in patients with type 1 diabetes are not different from normals. There is one value from the study of Merzouk et all (31) we have to take out and discuss. As we mentioned above Merzouk et all (31) measured lipoprotein profiles of two groups of pregnant women with type 1 diabetes. Firstly, woman with well- controlled insulin-treated type 1 diabetes and secondly, woman with poorly controlled type 1 diabetes. In Figure 10 C we can see a statistically higher triglyceride level in poorly controlled (group2) than in well controlled (group 1) diabetic women (31).

3.2 Fetal lipid and lipoprotein profile

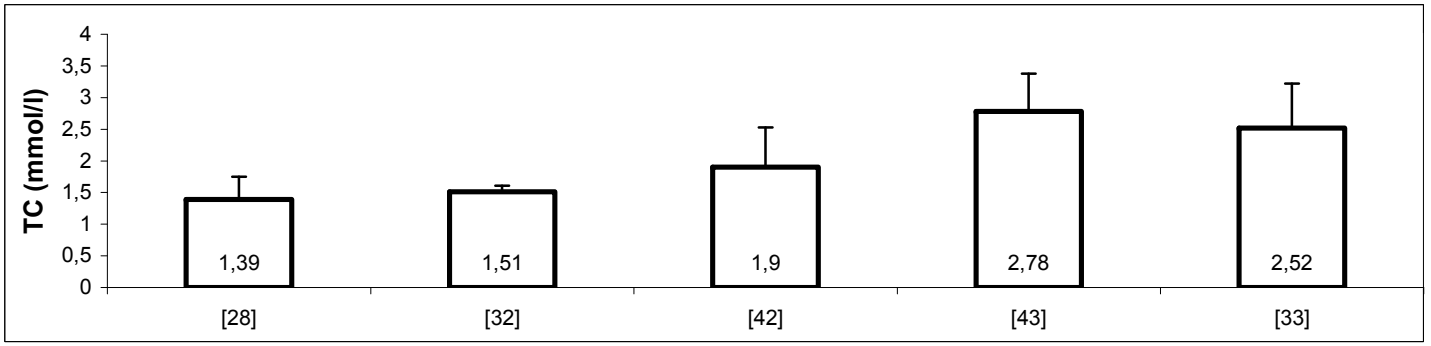
3.2.1 Total cholesterol concentrations

Figure 11 A: Fetal total cholesterol levels in controls



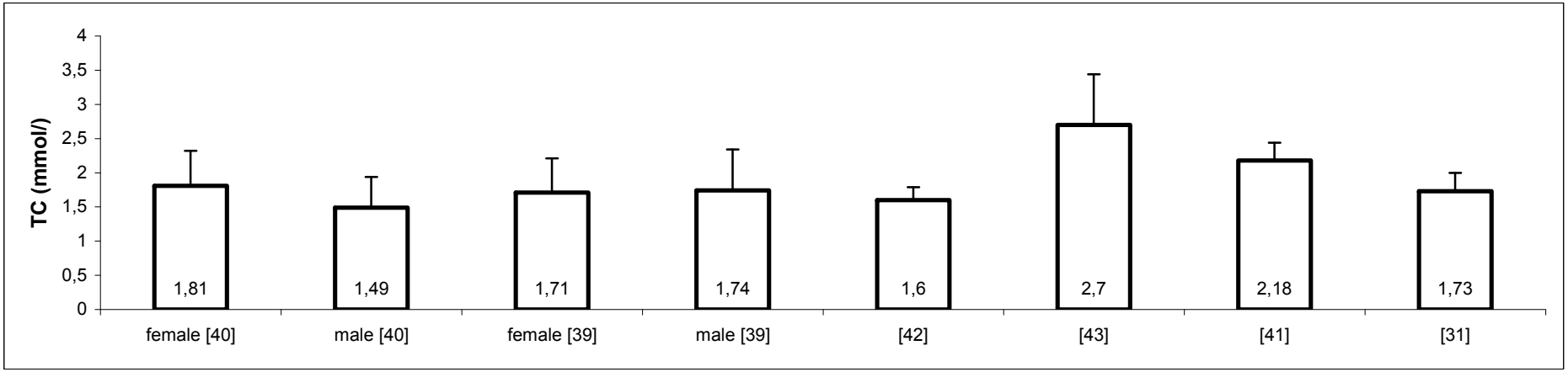
Mean fetal total- cholesterol levels in controls including all studies = **1,85 ± 0,33 mmol/l**

Figure 11 B: Fetal total cholesterol levels in GDM



Mean fetal total- cholesterol levels in GDM including all studies = **2,02 ± 0,61 mmol/l**

Figure 11 C: Fetal total cholesterol levels in IDDM



Mean fetal total- cholesterol levels in IDDM including all studies = **1,87 ± 0,39 mmol/**

Figure 11 A shows cord plasma total cholesterol levels in neonates with no prenatal and perinatal risk and whose mothers had normal fasting blood glucose and OGTT levels. It can be seen, that there are no significant differences in total cholesterol levels in infants of non diabetic mothers in the compared published studies, except the values in the study of Akisü et al (43) and Bukulmez et al (33). Akisü et al (43) measured significantly higher fetal total cholesterol levels compared to others. Compared with Couch et al (28), the study of Akisü et al (43) found 1.8- fold to 2- fold higher total cholesterol levels of neonates of non diabetic as well as of diabetic mothers (Figures 11 A, 11 B). A possible reason for this difference could be the different way of measurement the authors used. In Akisü et al (43) total cholesterol concentrations were measured by Hitachi 705 auto analyser using kits of Boehringer Mannheim (Germany) by enzymatic Chorlpap and glycerol- phosphate oxidase techniques whereas in Couch et al total cholesterol were determined by spectrophometric analysis. Different analytical methods are possible factors which can influence the result.

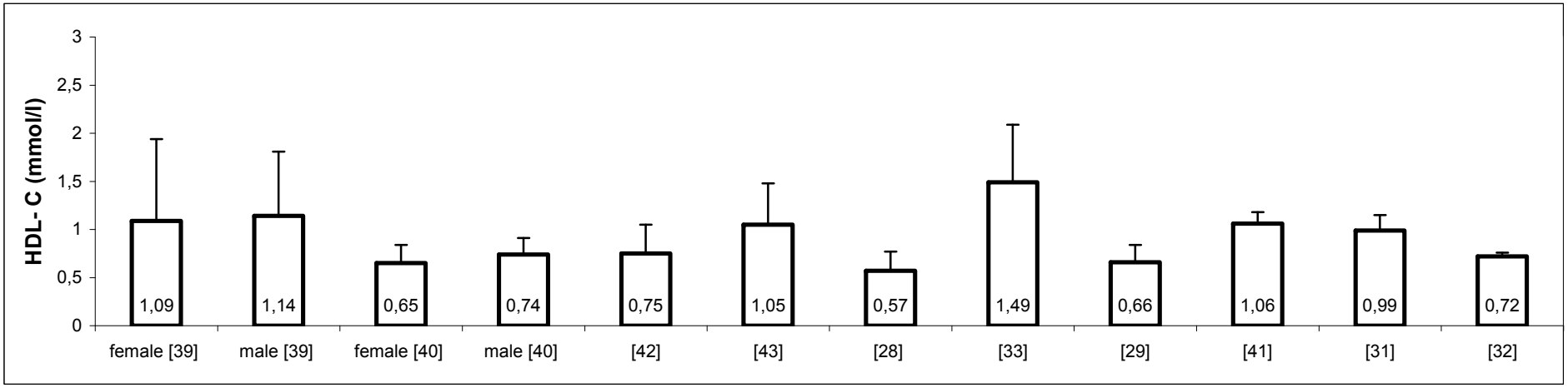
There are no differences in measured total cholesterol levels between the study of Abou Ghalia et al (42), an Egyptian study and European and American studies (31, 39, 40, 41). Abou Ghalia et al (42) found 1.2- to1.4- fold lower total cholesterol levels in controls compared to Sobki et al (32), a Saudi Arabian study and Bukulmez et al (33), a Turkish study. These findings led to the assumption that fetal total cholesterol levels in controls are independently from ethnic origin.
As it can also be seen in Figure 11 A, Fordyce et al (39) and Nelson et al (40) compared total cholesterol levels in infants of both sexes, male and female. Their data don't differ from each other significantly and both found no differences between male and female total cholesterol concentrations.

In Figures 11 B and 11 C we can see no significant increase in total cholesterol levels in infants of diabetic mothers compared to those of nondiabetic mothers. These results may attribute to a relatively good managed food intake as well as to a good maternal metabolic glycemic control as a strictly monitoring by regular measurements of blood glucose throughout pregnancy.
Within studies the total cholesterol levels between GDM, IDDM and control fetuses revealed no significant differences. Consistently with the cholesterol levels in controls

also in GDM and IDDM population Akisü et al (43) measured higher levels than the others did. This increase in higher cholesterol levels is more pronounced in the IDDM group compared to the other studies (Figure 11 C). This can be caused by the relatively small population size, which Akisü et al (43) included in their study. They included three groups of newborns in their study. Group 1 consisted of 7 infants of mothers with IDDM, group 2 of 18 infants of mothers with GDM and group 3 of 20 control infants with no prenatal and perinatal risk and whose mothers had no history of diabetes mellitus.

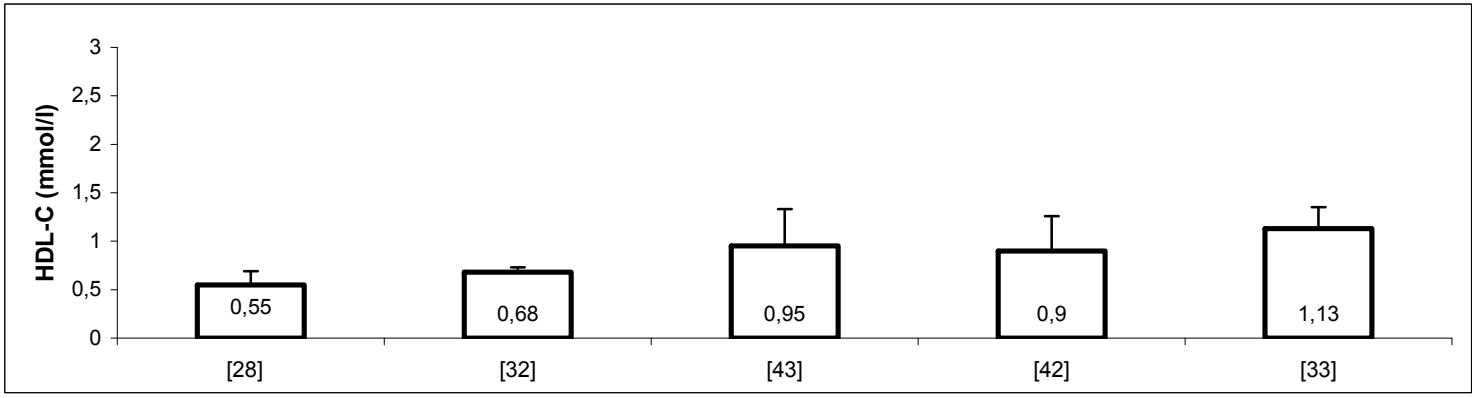
3.2.2 HDL- cholesterol concentrations

Figure 12 A: Fetal HDL- cholesterol levels in controls



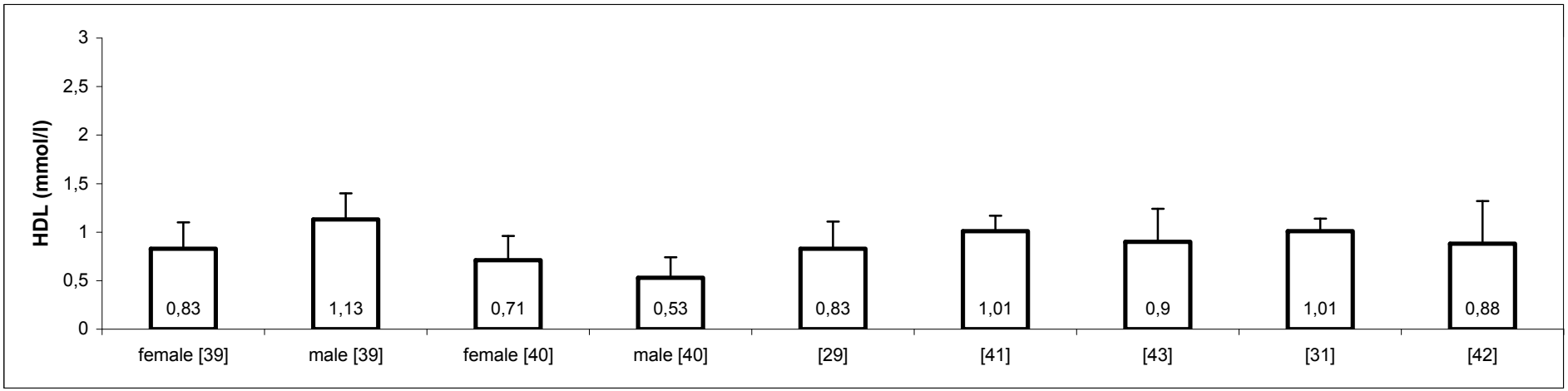
Mean fetal HDL- cholesterol levels in controls including all studies = **0,91 ± 0,27 mmol/l**

Figure 12 B: Fetal HDL- cholesterol levels in GDM



Mean fetal HDL- cholesterol levels in GDM including all studies = **0,84 ± 0,23 mmol/l**

Figure 12 C: Fetal HDL- cholesterol levels in IDDM



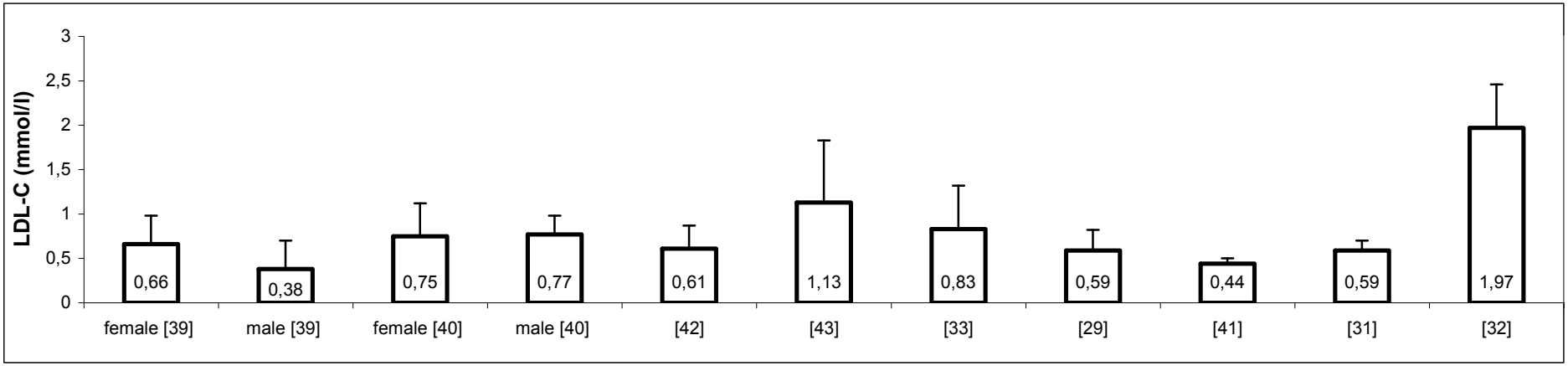
Mean fetal HDL- cholesterol levels in IDDM including all studies = **0,87 ± 0,18 mmol/l**

Fetal HDL- cholesterol levels in controls are given in Figure 12 A, with a mean value of 0.91 ± 0.27 mmol/l. There are no differences between the described studies, except in the study of Bukulmez et al (33), where the investigators measured 2.6- fold higher fetal HDL- cholesterol levels compared to the study of Couch et al (28). This obvious discrepancy could be explained by the different ethnic origin of the mothers the authors included in their studies. The study of Couch et al (28) took place in the United States of America and the authors measured lipid and lipoprotein concentrations of neonates of white mothers. In contrast, Bukulmez et al (33) and Akisü et al (43) are both Turkish studies. Following the results in Figure 12 A we guess that ethnic origin is an important determinant factor of changes in serum lipid and lipoprotein concentrations as well as in mothers and neonates.

Both, infants of mothers with GDM and infants of mothers with IDDM showed a slight but not significant reduction in HDL- cholesterol levels (Figure 12 B and 12 C).

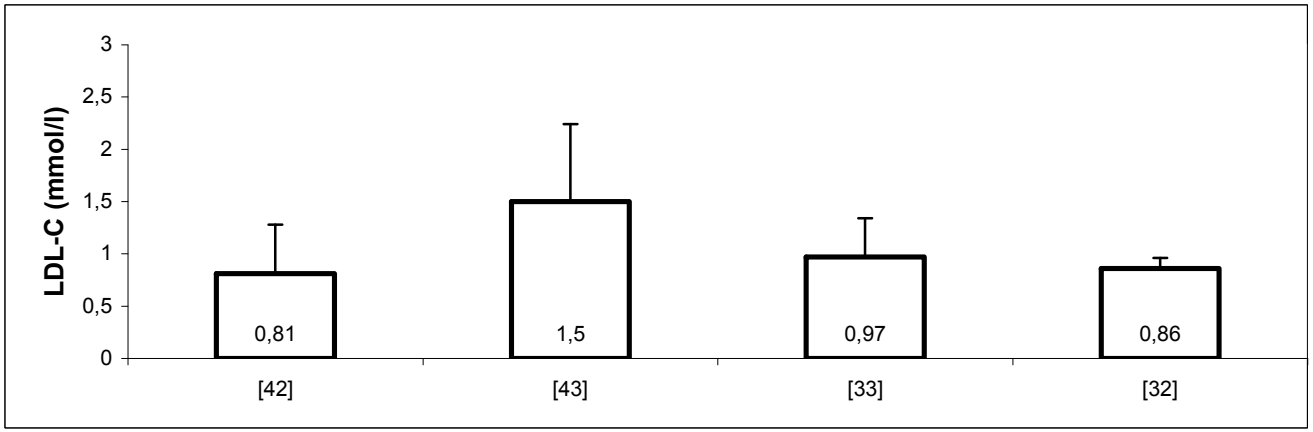
3.2.3 LDL-cholesterol concentrations

Figure 13 A: Fetal LDL- cholesterol levels in controls



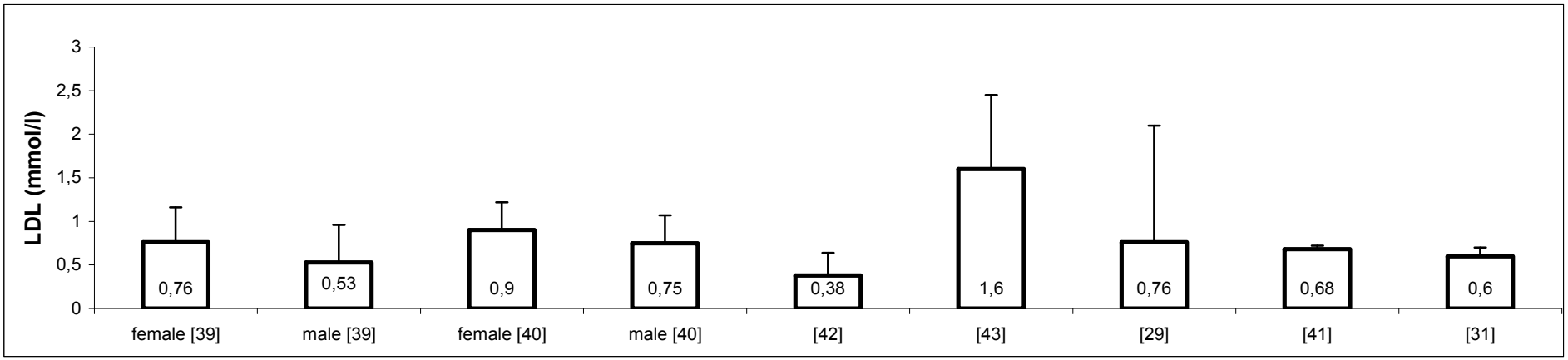
Mean fetal HDL- cholesterol levels in controls including all studies = **0,79 ± 0,44 mmol/l**

Figure 13 B: Fetal LDL- cholesterol levels in GDM



Mean fetal HDL- cholesterol levels in GDM including all studies = **1,04 ± 0,32 mmol/l**

Figure 13 C: Fetal LDL- cholesterol levels in IDDM

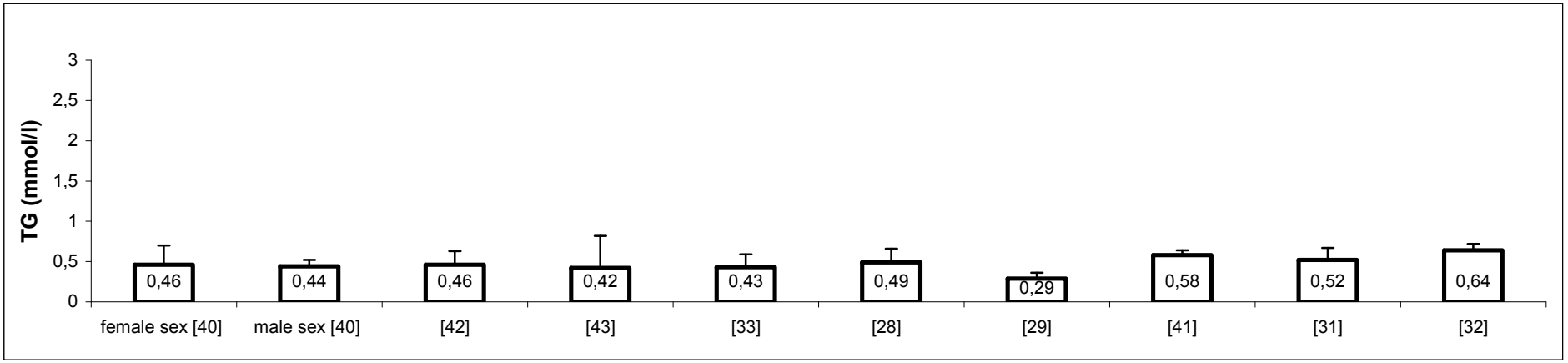


Mean fetal HDL- cholesterol levels in IDDM including all studies = **0,77 ± 0,35 mmol/l**

Figures 13 summarize results for LDL- cholesterol concentrations [mmol/l] in fetuses of diabetic and nondiabetic mothers. No convincing differences in LDL- cholesterol between fetuses nondiabetic mothers and fetuses of mothers with GDM or IDDM, except in the study of Sobki et al (32). Compared to others Sobki et al (32) measured 2.5- fold higher LDL- cholesterol concentration in control infants, whereas in GDM a 1.2 fold lower LDL- cholesterol concentration in infants of GDM mothers. Unfortunately, we cannot explain these differences that Sobki et al (32) found.

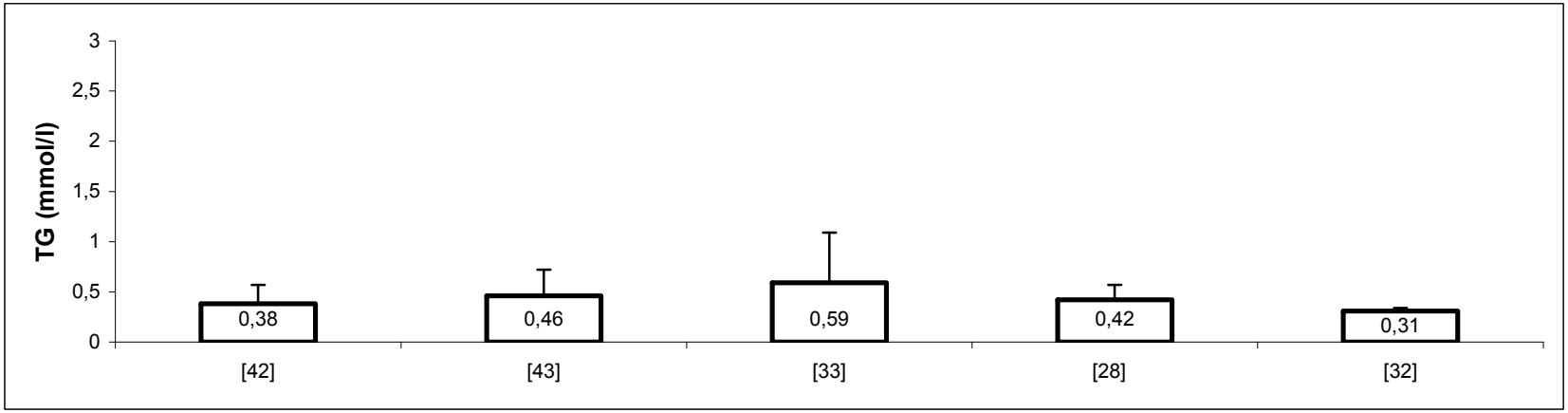
3.2.4 Triglyceride concentrations

Figure 14 A: Fetal triglyceride levels in controls



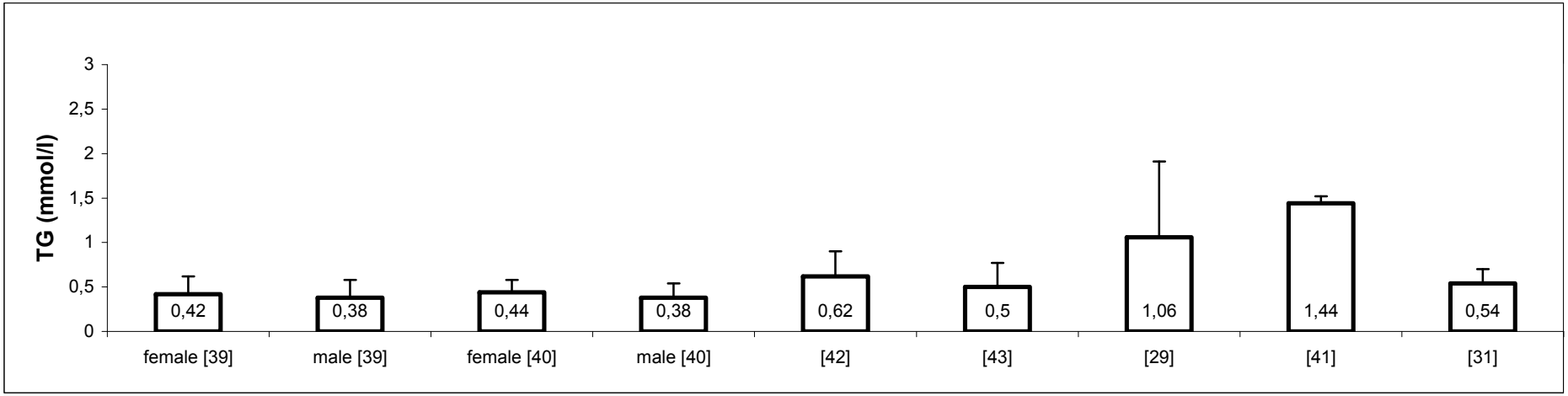
Mean fetal triglyceride levels in controls including all studies = **0,47 ± 0,09 mmol/l**

Figure 14 B: Fetal triglyceride levels in GDM



Mean fetal triglyceride levels in GDM including all studies = **0,43 ± 0,11 mmol/l**

Figure 14 C: Fetal triglyceride levels in IDDM



Mean fetal triglyceride levels in IDDM including all studies = **0,59 ± 0,27 mmol/l**

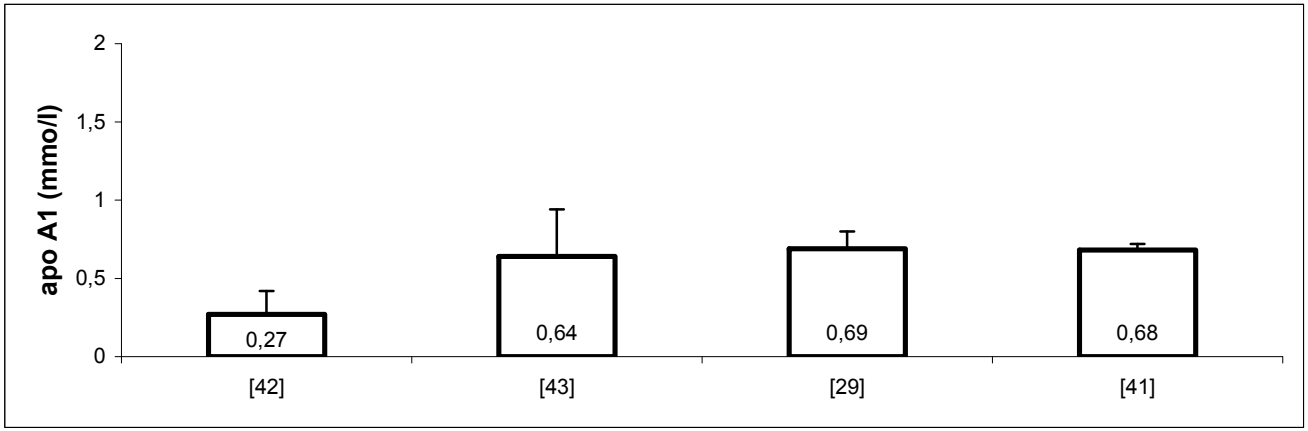
Figures 14 demonstrate triglyceride levels in blood from umbilical cord of fetuses of nondiabetic and diabetic mothers. In Figure 14 A all studies revealed similarly concentrations, except in the studies of Sobki et al (32) and Kilby et al (29). Sobki et al (32) measured a 2- fold higher fetal triglyceride level in controls compared to the study of Kilby et al (29). Both authors obtained blood samples from the umbilical vein before placental separation. The discrepancies between the two studies can be put down to different blood samples storing. Kilby et al (29) drawn their blood samples into plain and EDTA- containing tubes on ice and Sobki et al (32) drawn their blood samples into plain and Heparin- containing tubes.

Sobki et al (32) studied 40 blood samples of infants of mothers with normal pregnancy (controls) and 19 blood samples of infants of mothers with gestational diabetes under insulin treatment. They found a 2- fold decreased plasma concentrations of triglyceride in infants of mothers with gestational diabetes mellitus. Their results are differently from those of Akisü et al (43) and Couch et al (28), who reported consistently low triglyceride levels (Figure 14 B). This difference among these studies may be the result of smaller sample size, as well as methodological differences.

Figure 14 C shows triglyceride concentrations in neonates of mothers with insulin dependent diabetes mellitus. Nelson et al (40) and Merzouk et al (31) did not find differences in triglyceride concentration between newborns of mothers with or without insulin dependent diabetes mellitus. In comparison with their results, Merzouk et al (41) measured a 2.5 – fold increase in triglyceride concentration in newborns of mothers with IDDM compared with newborns of nondiabetic mothers. The study of Merzouk et al (41) was focused only on determining lipoprotein metabolism alterations in macrosomic infants (birth weight = 4840 ± 105g at term) of insulin dependent diabetic mothers at birth. Fat and protein syntheses are increased in the fetus with overnutrition and this data are in agreement with earlier reports (44, 45). The concomitant presence of excess substrates and hyperinsulinaemia enhances fetal lipid syntheses. Insulin receptors may also play a role in the increased effects in infants. Several authors have found evidence of defective downregulation of insulin receptors in the hyperinsulinaemic fetus, which may have increased insulin binding and thus its metabolic effects (46, 47). We suggest that this could be an explanation for the discrepancies among the studies.

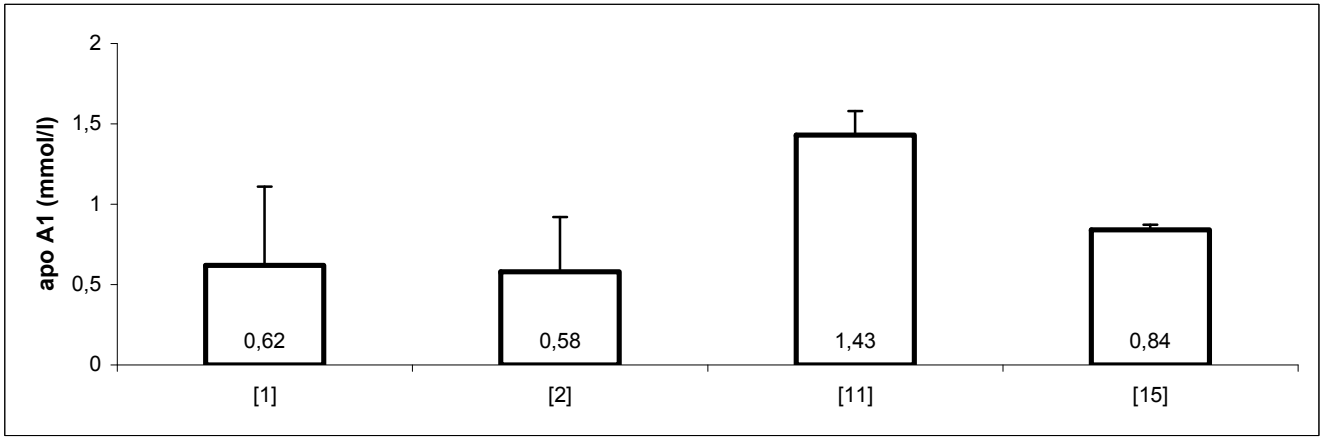
3.2.5 Apo A1 concentrations

Figure 15 A: Fetal apo A1 levels in controls



Mean fetal apo A1 levels in controls including all studies = **0,57 ± 0,21 mmol/l**

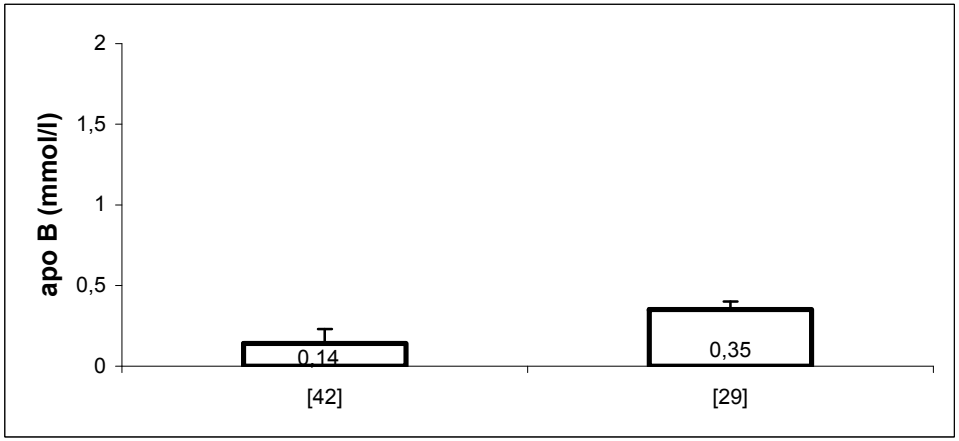
Figure 15 B: Fetal apo A1 levels in IDDM



Mean fetal apo A1 levels in IDDM including all studies = **0,87 ± 0,39 mmol/l**

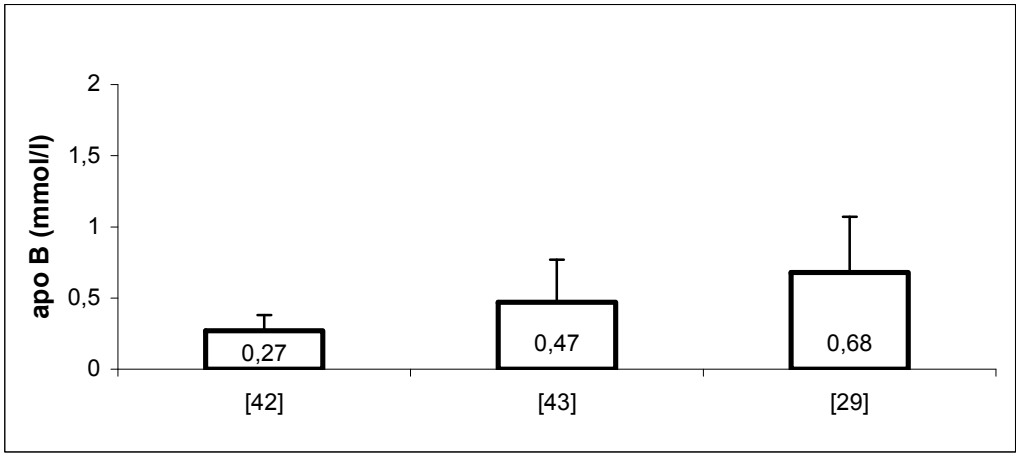
3.2.6 Apo B concentrations

Figure 16 A: Fetal apo B levels in controls



Mean fetal apo B levels in IDDM including all studies = **0,25 ± 0,15 mmol/l**

Figure 16 B: Fetal apo B levels in IDDM



Mean fetal apo B levels in IDDM including all studies = **0,47 ± 0,21 mmol/l**

Only two organs in the human body are shown to have major capatabilities for apoprotein synthesis, the liver and the small intestine (48). Quantitation of cord serum apoproteins showed that all known and well-characterized plasma apolipoprotein are present, but at lower levels than found in the normal adult (49).
Apolipoproteins ApoB, ApoD and C-III were the most reduced, whereas C-I, C-II, and ApoE were present were present at levels approaching those in adults, indicating sufficient quantities to perform their respective functions (50). Generally only few studies investigated apolipoprotein concentrations in the fetal circulation till now. Beyond all, here investigated studies demonstrated around 30 to 50% higher apolipoproteins levels in the IDDM seras compared to controls. In particular mean apoA1 concentrations in IDDM´s were 0.87±0.39 mmol/l vs 0.57±0.21 mmol/l in controls and apoB levels in IDDM´s were 0.47±0.21 vs 0.25±0.15 mmol/l, respectively. These findings in the present studies are consistent with the hypothesis that the increased level of the antiatherogenic ApoA1 in fetal blood may contribute to the vascular protection in the fetal circulation, which is more pronounced in the IDDM group and leading to good fetal growth. However, the higher amount of apoB levels in the IDDM group contrasts this hypothesis. Therefore it would be interesting whether the ratio of ApoB/A1 is altered in these studies because this ratio is a better indicator for metabolic risks.
In one study (42), the fetal apoA1 in controls showed significant lower levels compared to the three other studies (0.27 vs 0.68 mmol/l). This loss of ApoA1 from HDL, because the amount of free ApoA1 in fetal circulation is very small, can be explained by the analytical method the authors used. Kunikate et al (51) argued that the content of apoA1 remaining with the HDL complexes is influenced by repeated (ultra)centrifugation of the serum.
In conclusion the selected studied demonstrated that levels of fetal plasma apoproteins are altered in IDDM mothers. Whether the alterations of ApoA1 and ApoB is a causal or permissive factor for vascular diseases remains to be established.

4 Conclusion

Before making a general statement regarding lipid and lipoprotein management during pregnancy once has to verify study protocol, methods and sample size. A remarkable difference in methods between all studies was the different analytical methods, which the authors used. To achieve homogeneous parameters, standardisation in analytical methods is desirable. The studies should consider the type of diabetes mellitus, the degree of metabolic control and the ethnic origin in pregnant mothers in one hand as well as the gender and body weight of their neonates on the other hand.

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Project schedule

Spring 08

- Choosing a topic in Mugthesis
- Contacting supervisor
- Devising a concept and formulating an appropriate title
- Submitting concept form to Medical University

Summer 08

- Literature search
  Via pubmed and Library of Medical university Graz

  key words: mother, fetal, pregnancy, lipoprotein, total cholesterol, LDL, HDL, Diabetes, IDDM, GDM
  Lipid metabolism

Autumn/Winter 08

- Completing data
- Making an overview over all studies
- Summarizing values in distinct figures with regular feedback by the supervisor

Spring 09

- Writing the thesis with regular feedback by the supervisor

CURRICULUM VITAE, 2009

Chahira Moussa
Grazerstrasse 281/08, 8121 Deutschfeistritz
+43- (0) 650 3205944
Shahira_moussa84@yahoo.de

Date of Birth: 28.03.1984
Place of birth: Darna/ Libya
Nationality: Austrian/ Lebanese

EDUCATION:

October 2008	started with third term, Trainee Year at Trauma surgery University Clinic Graz; Internal Medicine, University Nephrology Clinic Graz; general practitioner, Helga Grablowitz, Judendorf- Strassengel and currently at University Gynaecology and Obstetrics Clinic Graz
September 2008	Completion of second term
May 2004	Completion of first term
October 2002	Medical studies at Medical University Graz
1998- 2002	High School, Bundesoberstufenrealgymnasium Eisenerz, scientific class, Matura (qualificationfor university entrance) in subjects German, Math, English and Biology

EXPERIENCES:

Work Experience:

September 2008	Medical Clerkship in Internal Medicine, KH der Barmherzigen Brüder, Graz – 2 weeks
July 2008	Medical Clerkship in Gynaecology and Obstetrics, University Gynaecology and Obstetrics Clinic Graz – 4 weeks
March 2008	Medical Clerkship in Internal Medicine, KH der Elisabethinen, Graz – 2 weeks
September 2007	Medical Clerkship in Gynaecology, KH der Barmherzigen Brüder, Graz - 4 weeks
February 2006	Medical Clerkship in Internal Medicine, Dr. Michael Mandak, Gratkorn – 2 weeks
September 2006	Medical Clerkship in Internal Medicine, University Rheumatology Clinic Graz – 2 weeks

Languages:

Arabic	First mother tongue
German	Second mother tongue
English	fluently

Computer literacy:

Microsoft Office (Word, Excel, PowerPoint), Citavi