Determinants of Placental Growth in vivo

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Graz, 2 Juni 2009 ………………………………….

Eidesstattliche Erklärung

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Graz, am 2 Juni 2009

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The first person I would like to thank is certainly my supervisor Prof. Dr. Gernot Desoye. He offered me the opportunity to write this thesis on determinants of placental growth in vivo.

He supported my work, introduced me into science-based working and guided me through all difficulties of writing this thesis.

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ABSTRACT:

Introduction: The placental weight is a significant parameter reflecting fetal development during pregnancy and, on a population basis, may predict the development of diseases in adulthood, nevertheless it receives less attention throughout pregnancy in obstetrics in contrast to the fetal weight

Methods: This thesis reviews 54 articles of primary medical literature as well as of international databases like the PubMed published between 1956 and February 2009. Different variables such as the mode of preparation, the gender of the newborn, parity, multiple gestations, ethnicity, maternal nutrition and maternal exercise during gestation and their effect on placental weight has been analyzed.

Results: The mode of preparation before weighing has a major influence on the placental weight. The average weight difference between trimmed and untrimmed, which are heavier, placentas is 16 per cent. Placenta weights of male infants tend to be slightly higher than placenta weights of female infants. Moreover parity has a major influence on the placental weight. Placentas of first pregnancies show a significantly lower weight than placentas of multiparous women. In case of twin pregnancies the mean value of the placental weight per fetus is on average 74g and in triplet pregnancies 117g lower than the placental weight in singleton pregnancies. In addition ethnicity influences placental weight as well. Europeans, specifically Caucasians, show higher placental weights as compared to the Asian population. A further aspect, which influences placental weight, is maternal nutrition. Mild maternal undernutrition throughout early pregnancy has a positive effect on placental growth and leads to increased placental weight, whereas high energy intake in the first trimester is associated with lower placental weights. Also maternal exercise during gestation influences placental development. A significantly greater placental volume has been observed in women, who regularly performed 20 minutes of weight-bearing exercise throughout pregnancy. However, an intensity increase of exercise in late pregnancy has been associated with a decrease of placental weight.

Conclusion: In addition to the genetic make up of the fetus a range of maternal factors have an effect on placental development and weight. The placenta should be monitored throughout pregnancy, because pathologic changes in placental development will affect fetal growth. Placental weight can serve as an indicator for placental and hence fetal growth.

KURZFASSUNG:

Einleitung: Das Plazentagewicht ist ein signifikanter Parameter, der die fetale Entwicklung in der Schwangerschaft widerspiegelt und für die Wahrscheinlichkeit der Entstehung von Krankheiten im späteren Leben Aussagekraft haben kann. Dennoch wird es in der Geburtshilfe noch weit weniger beachtet als das fetale Gewicht.

Methoden: Als Grundlage dieser Arbeit dienen 54 Artikel aus medizinischer Basisliteratur und internationalen Datenbanken, wie zum Beispiel PubMed, die zwischen 1956 und Februar 2009 veröffentlicht wurden. Verschiedene Variablen, wie die Art der Präparation, das Geschlecht des Neugeborenen, die Parität, Mehrlingsschwangerschaften, Ethnizität, mütterliche Ernährung und mütterliche-körperliche Ertüchtigung während der Schwangerschaft und ihr Einfluss auf das Plazentagewicht sind untersucht worden.

Ergebnisse: Die Art der Präparation vor dem Wiegen hat großen Einfluss auf das Plazentagewicht. Der durchschnittliche Gewichtsunterschied zwischen unbehandelten, die schwerer sind, und präparierten Plazenten beträgt 16 Prozent. Das Plazentagewicht von männlichen Neugeborenen ist üblicherweise geringfügig höher, als das weiblicher Neugeborener. Darüber hinaus hat die Parität großen Einfluss auf das Plazentagewicht. Plazenten erster Schwangerschaften haben ein signifikant geringeres Gewicht als jene Mehrgebärender. Im Falle von Zwillingsschwangerschaften ist das mittlere Plazentagewicht pro Fetus um 74g bzw. im Falle von Drillingsschwangerschaften um 117g niedriger im Vergleich zu Einlingsschwangerschaften. Weiters beeinflusst die Ethnizität das Plazentagewicht. Bei Europäern bzw. bei Weißen ist im Vergleich zu Asiaten ein höheres Plazentagewicht beobachtet worden. Ein zusätzlicher Aspekt, der das Plazentagewicht beeinflusst, ist die mütterliche Ernährung. Es ist beschrieben worden, dass sich eine leichte mütterliche Unterernährung während der frühen Schwangerschaft positiv auf das Plazentawachstum auswirkt und zu einem höheren Plazentagewicht führt. Hingegen führt eine hohe Kalorienzufuhr im ersten Trimester zu einem geringeren Plazentagewicht. Ein weiterer Faktor, der die Entwicklung der Plazenta beeinflusst, die ist körperliche Ertüchtigung der Mutter. Bei Müttern, die regelmäßig ein 20-minütiges Training während der Schwangerschaft absolviert haben, konnte ein erhöhtes Plazentavolumen beobachtet werden. Es konnte jedoch eine Intensitätserhöhung in der späten Schwangerschaft mit einer Abnahme des Plazentagewicht in Zusammenhang gebracht werden.

Fazit: Zusätzlich zu genetischen Komponenten haben auch einige unterschiedliche Faktoren einen Einfluss auf die Entwicklung der Plazenta und damit auf das

Plazentagewicht. Dieses sollte während der Schwangerschaft wiederholt überprüft werden, da pathologische Veränderungen der Plazentaentwicklung das fetale Wachstum beeinflussen.

CONTENTS:

Figure Index 8
Table index 10
1. Introduction 11
2. Material and Methods 15
3. Influence of different aspects on the placenta and child weight development: a review and comparison 16
- 3.1. Untrimmed vs. Trimmed placental weight 16
- 3.2. Singleton placental weight development 18
  - 3.2.1. Singleton Placental Weight Curves 19
  - 3.2.2 Placental weight increase per week of gestation 25
  - 3.2.3. Secular trend of placental weight 29
  - 3.2.4. Placental weight related to placental diameter 31
- 3.3. Gender specific placental weight 33
- 3.4. Placental weight depending on parity 36
- 3.5. Placental weight and birth weight 41
  - 3.5.1. Fetal-Placental weight ratio 44
  - 3.5.2. Placental weight in relation to birth weight category 49
- 3.6. Placental weight in twin and triplet pregnancies 52
  - 3.6.1. Placental weight increase per week 56
- 3.7. Influence of ethnicity on placental weight 57
- 3.8. Influence of maternal nutrition on placental weight 62
  - 3.8.1. Influence of maternal undernutrition on the placenta 71
  - 3.8.2. Influence of the maternal obesity on placental weight 76
  - 3.8.3. Influence of nausea and vomiting on placental growth 77
- 3.9. Influence of maternal exercise on placental weight 79

4. Summary and Discussion 82
Bibliography: 88

FIGURE INDEX

Figure 1: Comparison of data describing the placental development between the 8th and the 18th gestational week 19
Figure 2: Trimmed placental weight change between the 21st and the 41st gestational week........ 20
Figure 3: Placental weight development depending on the gestational age........ 21
Figure 4: Placental weight changes with gestational age between the 27th and the 41st gestational week 22
Figure 5: Placental weight change between the 8th and 40th pregnancy week 23
Figure 6: Placental weight development between the 23rd and the 27th pregnancy week 24
Figure 7: Comparison of weight changes of trimmed placentae........ 25
Figure 8: Comparison of biweekly placental weight increase between the 8th and the 40th gestational week 27
Figure 9: The calculated biweekly mean placental weight increase in the first and the second half of pregnancy........ 27
Figure 10: Overview of the untrimmed placental weight change from 1891 to 2002 30
Figure 11: Relationship of the placental weight and the placental diameter 31
Figure 12: Placental weight and its association with the placental diameter 32
Figure 13: Comparison of sex specific untrimmed placental weights between the 32nd and the 42nd pregnancy week 33
Figure 14: Comparison of untrimmed sex specific placenta weights between the 24th and the 44th gestational week 34
Figure 15: Placental weights depending on parity delivered between the 34th-42nd gestational weeks 37
Figure 16: Sex specific placental weights depending on parity 38
Figure 17: Untrimmed placental weights depending on parity and gender of the neonate delivered between the 32nd and the 42nd gestational week........ 39
Figure 18: Placental weight compared to embryonic/fetal weight between the 8th and the 22nd pregnancy week 42
Figure 19: Placental weight compared to birth weight between the 8th and the 40th gestational week........ 43

Figure 20: Fetal-placental weight ratio between the 22nd and 42nd gestational week...... 45
Figure 21: Fetal-placental weight ratio 46
Figure 22: Placental weight development associated with the infants size........................ 50
Figure 23: Trimmed twin placental weight between the 19th and the 41st gestational week 52
Figure 24: Trimmed triplet placental weight between the 20th and the 38th pregnancy week 53
Figure 25: Comparison of trimmed singleton, twin and triplet placental weights between 21st and the 38th week 54
Figure 26: Trimmed singleton and twin placental weight comparison between the 23rd and the 27th pregnancy week 55
Figure 27: Comparison of the biweekly placental weight increase in singleton, twin and triplet pregnancies 56
Figure 28: Placental weight associated with white and black ethnicity between the 27th-44th gestational week 57
Figure 29: Comparison of trimmed placental weight related to ethnicity between the 34th -42nd gestational week.. 58
Figure 30: Untrimmed placental weight associated with ethnicity delivered between 39th - 41st pregnancy weeks 59
Figure 31: Relationship of trimmed placental weight and ethnicity between the 37th-42nd pregnancy weeks.. 60
Figure 32: Placental weight depending on maternal energy, carbohydrate, fat and protein intake in early pregnancy 63
Figure 33: Placental weight related to maternal energy, carbohydrate, fat, protein, vitamin C, vitamin E and folate intake in early gestation 65
Figure 34: Placental weight depending on maternal energy, carbohydrate, fat and protein intake in late pregnancy 67
Figure 35: Placental diameter and birth weight related to caloric intake in the 3rd trimester... 68
Figure 36: Placental diameter and birth weight related to protein/carbohydrate intake in the 3rd trimester 69
Figure 37: Placental and birth weight development during the Dutch famine in the Western part 74

Figure 38: Placental and birth weight development during the Dutch famine in the Northern part 74
Figure 39: Trimmed placental weight in association with nausea and vomiting of pregnancy 78
Figure 40: Modified version of a placental and birth weight development scale depending on the level of exercise in late pregnancy 80
Figure 41: Changes of a placental volume over the second half of gestation depending on exercise 81

TABLE INDEX

Table 1: Comparison of the weight differences percentage between untrimmed and trimmed placentas 17
Table 2: Placental weight increase per week 26
Table 3: Overview of the change of placental weight since 1891 29
Table 4: Comparison of male and female placental weight and their weight difference in % 35
Table 5: Placental weight changes associated with the infants size 49
Table 6:Comparison of singleton, twin and triplet placental weights 54
Table 7: Comparison of the fetal-placental weight ratio in association with ethnicity... 60
Table 8: Placental and birth weight depending on maternal energy, carbohydrate, fat and protein intake in early pregnancy 62
Table 9: Placental and birth weight depending on maternal energy, carbohydrate, fat and protein intake in late pregnancy 66
Table 10: Placental diameter and birth weight depending on the caloric intake in the 3rd trimester 68
Table 11: Placental diameter and birth weight related to Protein/carbohydrate intake in the 3rd trimester 69
Table 12: Birth weight and placental weight development during the Dutch famine....... 72
Table 13: Overview of influencing factors in association with high and low placental weight 86

1. INTRODUCTION

In obstetrics the relationship of birth weight and the perinatal outcome has long been appreciated, however an often neglected parameter is the weight of the placenta, an organ which plays a key role for fetal growth. The placenta consists of two parts: the maternal part anchoring it in the uterus, and the fetal surface, connected to the fetus through the umbilical cord. It acts as an interface between the maternal and the fetal circulation. Furthermore the placenta accounts for the exchange of oxygen and carbon dioxide, nutrients, degradation products and immunoglobulin. At the end of term about 10-15m² total placental surface area are available for exchange. In addition the placenta produces hormones which are important for maintenance of pregnancy like the human chorionic gonadotropin, human placental lactogen and steroids as progesterone and estrogens (Pocock and Richards 2006; Guyton and Hall 2006; Stauber and Weyerstrahl 2007).

An adequate placental development and placental growth is the basis for a favorable fetal development.

Six days after fertilization the blastocyts reaches the uterus, where it attaches to the endometrial surface of the fundus uteri. The outer cells of the blastocyts differentiate to the trophectoderm and, subsequently, develop to trophoblasts, which are responsible for the invasion of the endometrium and building up of the placenta; the cells inside the blastocyt differentiate in to the embryoblast which is the basis of fetal development.

The trophoblast differentiates into an internal cell layer, the cytotrophoblast, and an external cell layer, the syncytiotrophoblast. A proportion of cytotrophoblast invade into the endometrium and connect with the maternal spiral arteries. Thereafter maternal blood circulates into lacunae built by the syncytiotrophoblast. Sinuses with maternal blood build the intervillous space and surround the placenta villi that contain the fetal blood, where the exchange takes place. At the end of the first trimester of gestation the placental differentiation and development are almost completed. From there on the placenta will mostly growth in mass. 15-20 cotyledon divided by the placental septa develop on the placenta surface. A cotyledon is composed of a placental villus and intervillous space. The two parts that build the placenta´s maternal surface are the decidua basalis and uterine vessels.

The fetal surface of the placenta comprises of the endothelium lining fetal-placental vessels, the chorionic plate and the umbilical cord that are both covered by amnion (Sadler 1998; Pocock and Richards 2006).

Research over many years has shown that the development of placenta and the fetus represented by their weight through out pregnancy can serve as good indicators for perinatal outcome. In general the placental weight is a good measure for the placental size, the quality and efficiency of the placenta. Deviations from normal, i.e., ≤5th and ≥95th percentiles, weight are often associated with pregnancy pathologies.

To supervise, for example, growth retarded fetuses, birth weight percentile curves can assist the obstetrics. However placental weight percentile curves are uncommon in obstetrical practice and research. Because of the major influence of the placenta, which can easily limit the fetal development, it is necessary to know how the weight of normal placentas develops throughout gestation. Subsequently, by measuring or assessing the placental weight changes on gestation can be detected earlier which have an effect on the fetal growth.

It is reported that various diseases during pregnancy are associated with abnormal placental growth and, hence, weight:

For instance, abnormal low placental weights compared to fetal weight are associated with:

- maternal uteroplacental vascular insufficiency like maternal chronic or pregnancy-induced hypertension,
- preeclampsia,
- major malformations of the fetus.

Frequent causes of large placentas are:

- maternal diabetes mellitus,
- congenital syphilis,
- Rhesus incompatibility,
- chronic intrauterine infection,
- hydrops fetalis,
- maternal or fetal anemia.

In addition to its role in reflecting pregnancy development and fetal well being, the placental weight also has an influence on child development and plays a role in the development of diseases in adulthood. For example small placentas relative to gestational age cause high hemoglobin levels in neonates and further lead to lower body size at the

age of 7. On the other hand large placentas are associated with neonatal death, acute antenatal hypoxia and long term neurologic abnormalities. Humans who had a large placenta and low birth weight have a higher risk to develop cardiovascular disease later (Naeye 1987; Pinar et al. 1996; Williams et al. 1997).

When placenta weight shall be compared it is important to differentiate between the placental preparation methods, of which several are known and used nowadays. Therefore a direct comparison of reported placenta weight is difficult, because it is hard to estimate if the weight differences observed result from different methods of preparations or are true reflection of different placental weight.

Lots of effects like the gender of the newborn, parity, multiple gestations, maternal nutrition and maternal exercise during gestation influence the birth weight of the fetus. Moreover the social economic status and maternal smoking throughout pregnancy may influence the birth- and placental weight however these aspects were not taken into account in this thesis.

The birth weight of male neonates is usually higher than the birth weight of female neonates (Thomson et al. 1969). The weight difference can be detected from the 24 gestational weeks on and may end up with a mean difference of 140g at term (Bleker et al. 2006).

In addition birth weight differences are reported by associated with to parity. Neonates from first pregnancies usually have lower birth weights compared to neonates from second and third pregnancies (Thomson et al. 1969). The disagreement between the birth weight of children from primiparous to multiparous women at the end of term may be as high as 200g (Bleker et al. 2006).

A question that has not yet been sufficiently answered is: Can similar weight differences also be observed in the placenta? Is the placenta the limiting factor for the fetal development and weight gain in female neonates and neonates from primiparous women?

A problem that has been becoming more and more important is multiple pregnancies.

In the past multiple pregnancies were not so common but the situation has changed due to an increased rate of successful in-vitro-fertilizations. To make up for the higher abortion rate of zygotes that goes along with in a vitro fertilization several fertilized eggs are implanted in the uterus (Kiechle 2008). Which eventually may lead to multiple pregnancies, these are associated with several problems compared to singleton pregnancies. For example twins often have lower birth weights than singleton and are typically born earlier (Gielen et al. 2006; Bleker et al. 2006).

To allow for an unrestrained fetal development a sufficient nutrition exchange between the mother and the fetus need to be ensured. Another important factor that needs to be considered is nutrition itself both in terms of quality and quantity. How does maternal food intake before pregnancy and during the three trimesters of pregnancy influence the placental weight, and in consequence the fetal weight gain? In experimental studies in sheep, for instance, it was described that high nutrient intake during early gestation leads to a reduction in placental and fetal weight. Of more interest, however, is the effect of the alimentation of humans on placental development. How does maternal undernutrition during gestation influence placental as well as fetal growth? Should nutrition therefore be different in early and late pregnancies in order to support placental growth?

To answer all these questions several studies have been carried out. The purpose of the present work is to offer a wide overview by summarizing and comparing the results of these studies.

2. MATERIAL AND METHODS

The research focuses on the placental weight as a good and easily comparable measurement for placental size and as a proxy measurement for the quality and efficiency of the placenta.

The basic method used here was to review literature. Based on the article “Do placental weights have clinical significance” Naeye (1987) which describes independent variables influencing the placental weigh, the following variables were used for further search:

- Singleton pregnancies
- Placental weight percentile curves
- Multiple pregnancies (twin, triplet)
- Gender
- Parity
- Ethnicity
- Maternal nutrition
- Maternal exercise

In the literature two main measures, trimmed and untrimmed placenta weights are used. Results for both measures are presented whenever available. Guided by these influencing factors the research was performed in appropriate primary medical literature as well as in international databases like the PubMed.

Search criteria were `placenta weight´ combined with the factors listed above and the 'AND' conjunction. Overall 1043 papers were found with this method.

All these papers, published between 1956 and February 2009, were evaluated and only those with exact specification of the placental weight and the mentioned influences were used in this thesis. To simplify the comparison of placental attributes only placentas of uncomplicated pregnancies and sea level altitude were used. Based on the references in these papers further literature was found.

Eventually, 54 articles were used for analysis. The data on placental weight are visualized and the results are evaluated and compared.

3. INFLUENCE OF DIFFERENT ASPECTS ON THE PLACENTA AND CHILD WEIGHT DEVELOPMENT: A REVIEW AND COMPARISON

3.1. UNTRIMMED VS. TRIMMED PLACENTAL WEIGHT

When comparing placental weight data of different papers, an important factor to know, is the placental preparation before weighing. It needs to be considered that there is a placental weight difference between untrimmed and trimmed placentas. After removing the umbilical, the membranes and any blood clots the placenta is called trimmed placenta. A few authors tried to figure out how much the difference is. Placentas of 50 infants born at the Princess Anne Maternity Hospital, Southampton, were weighed before and after trimming. It is reported that the mean weight difference between untrimmed and trimmed placentas was 16.3%, about 5% are accounted for by the umbilical cord and about 10% by the membranes (Leary et al. 2003). Additionally the mode of delivery had a significant influence on the difference; untrimmed placental weight was 19% higher than trimmed placental weights for vaginal deliveries. Whereas in the case of caesarean section was 14% (Leary et al. 2003). A similar behavior was observed by Heinonen et al. (2001): 16.600 placentas were weighed after delivery between the 32nd and 43rd week. The placentas were cleared of blood and clots and were examined thereafter. They were weighed along with their membranes and the cords. More than 1500 placentas were weighed both trimmed and untrimmed. A discrepany with a factor by 17% between trimmed and untrimmed placental weight was observed (Heinonen et al. 2001). In another report the weight of trimmed placentas, (the membranes and the umbilical cord was trimmed and the blood was drained) was lower by a mean of 13.6% than the weight of untrimmed placentas (Dombrowski et al. 1994).

On the other hand Garrow (1970) reported that blood free placental weights are better suited to compare the effective functional capacity and amount of metabolically active protein

Table 1: Comparison of the weight differences percentage between untrimmed and trimmed placentas, data according to Leary et al. (2003), Heinonen et al. (2001), Dombrowski et al. (1994).

Untrimmed (g)	Trimmed (g)	%	Reference
589	480	16	Leary et al. (2003)
n.A.	n.A.	17	Heinonen et al. (2001)
n.A.	n.A.	14	Dombrowski et al. (1994)
		16	Average

n.A: data not available

Conclusion: Trimmed placentas have on average a 16% lower weight than untrimmed placentas.

3.2. Singleton placental weight development

How does the placental weight change throughout pregnancy?

The placental weight increases over the whole duration of gestation, but the rate of weight gain drops near term. Two periods of placental growth during the whole course of gestation were described. First the period of active cell division or hyperplastic growth, because of an increase of DNA content which is completed by 34-36th week of pregnancy (Rosso 1980, Younoszai et al. 1969). Thereafter the period of hypertrophic growth follows, where the cell size or protoplasmic mass increases which is reflected by an increase in protein/DNA or weight/DNA ratios. Furthermore a wide range of histological and morphological changes occur during gestation: Continuous formation and differentiation of villi with proportional expansion of the exchange surface area as well as progressive reduction in the thickness of placental membrane, including trophoblast, connective tissue and capillary endothelium (Rosso 1980).

It might therefore be concluded that proliferation is more important in the first half of gestation, while differentiation of the chorionic villous tree is more relevant in the second half of pregnancy.

In late gestation, placental function increases in regard to the rapid fetal growth in spite of the reduced growth rate of the placenta gain. However, trophoblast proliferation rate decreases from early gestation to term (Arnholdt et al. 1991).

Moreover the initially cell division prevails as an indicated by a proportional rise in DNA, RNA, and protein. The placenta increases proportionally in total weight, protein, and RNA until term. However the DNA content increases almost linearly only until placental weight reaches about 300 g (35-36th gestational week). Accordingly DNA content then remains virtually unchanged, cell division has stopped, the increase in cell size is associated with an increase in protein and RNA (Winick et al. 1967).

Others, however, described a steady increase in placental weight from the 24th to the 41st week of gestation (Hendricks 1964).

Another report on a placental weight increase throughout gestation, (until 42 weeks) with no evidence of a growth arrest in late gestation, supports this hypotheses (Molteni et al. 1978).

The placenta continues to gain weight throughout pregnancy, however its initial growth is much more rapid than that of the fetus. At the end of gestation it is appreciable that there is a slowing of the placental growth because the placenta reaches 90% of its final weight approximately 22 days before term (Hendricks 1964).

3.2.1. Singleton Placental Weight Curves

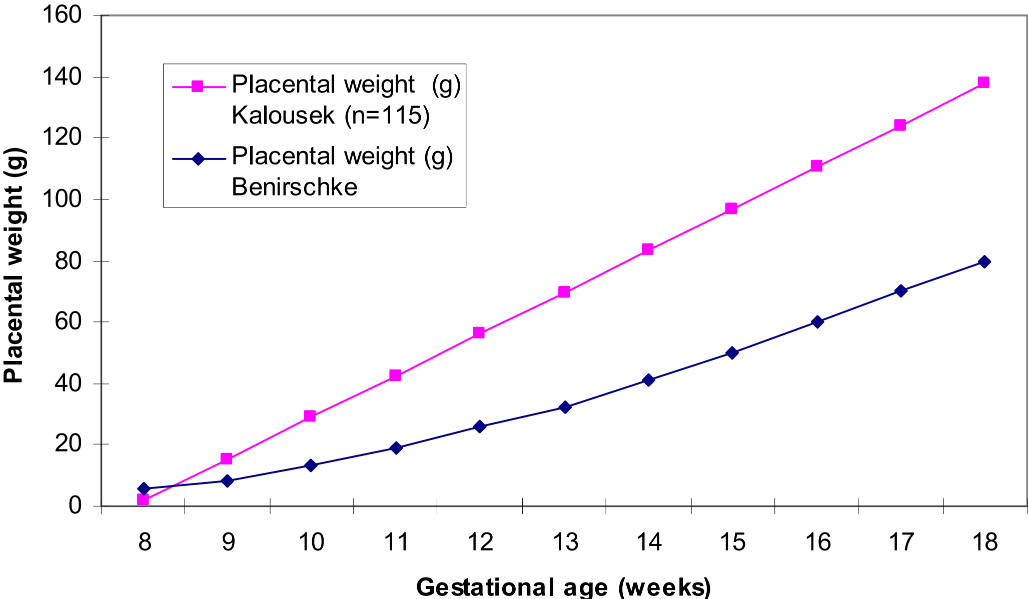


Figure 1: Comparison of data describing the placental development between the 8th and the 18th gestational week modified from Benirschke et al. (2006) [data in Benirschke were taken from several other publications in which number of samples per week was not reported] and Kalousek et al. (1990).

Figure 1 describes the comparison of two different placental weight curves between the 8th and the 18th gestational week. Both curves show an almost linear increase of placental weight up to the 18th week.

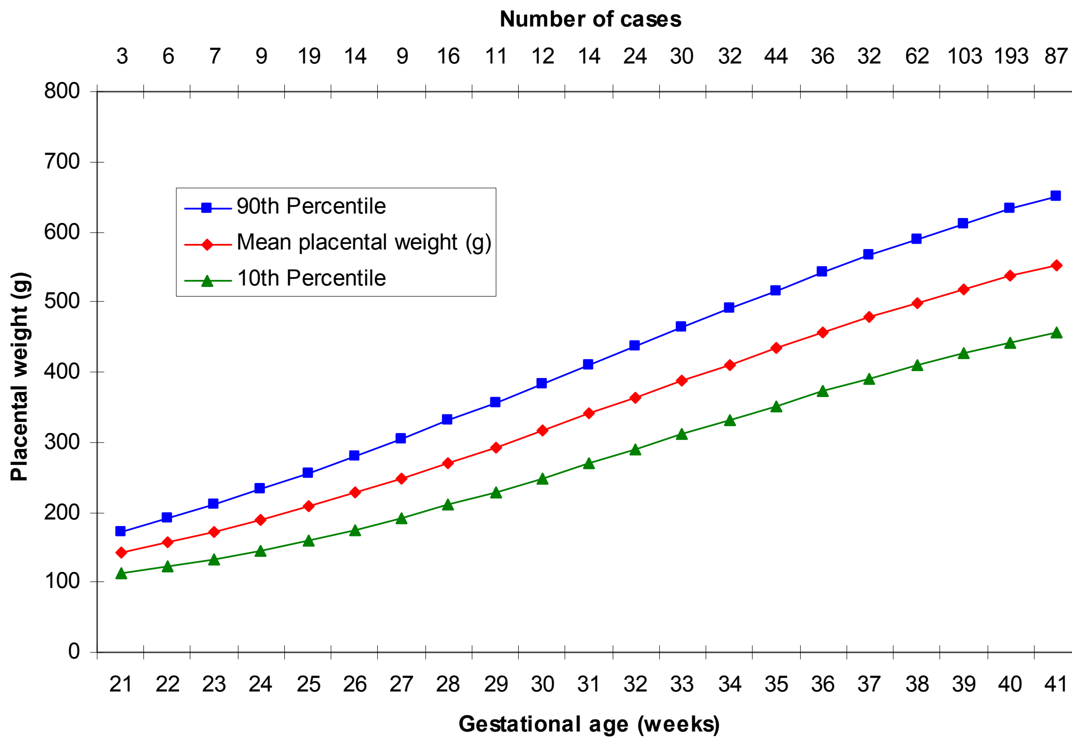


Figure 2: Trimmed placental weight (n=763) change between the 21st and the 41st gestational week modified from data of Pinar et al. (1996).

Figure 2 shows the placental weight of 763 trimmed placentas determined at an urban hospital at sea level between the 21st and the 41st gestational week.

The initial mean weight was 143g with a direct time dependent increase to final value of 553g.

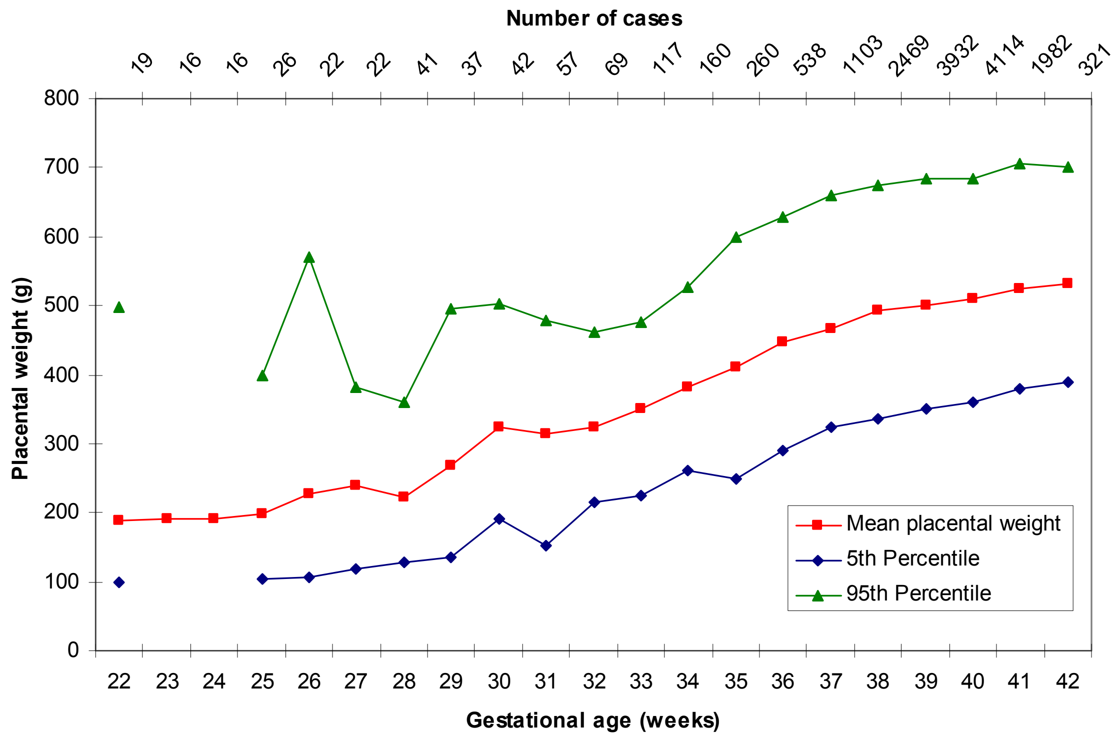


Figure 3: Placental weight development depending on the gestational age modified from Knaus et al. (2004).

Figure 3 shows the placental weights from 15,463 deliveries at Springfield, Massachusetts, between the 22nd to 42nd gestational weeks. These placentas were weighed fresh after trimming the cords and membranes. The mean placental weight (red) starts with a weight of 189g in the 22nd week. The weight increases almost linearly continuously throughout gestation with a final weight of 532g in the 42nd week.

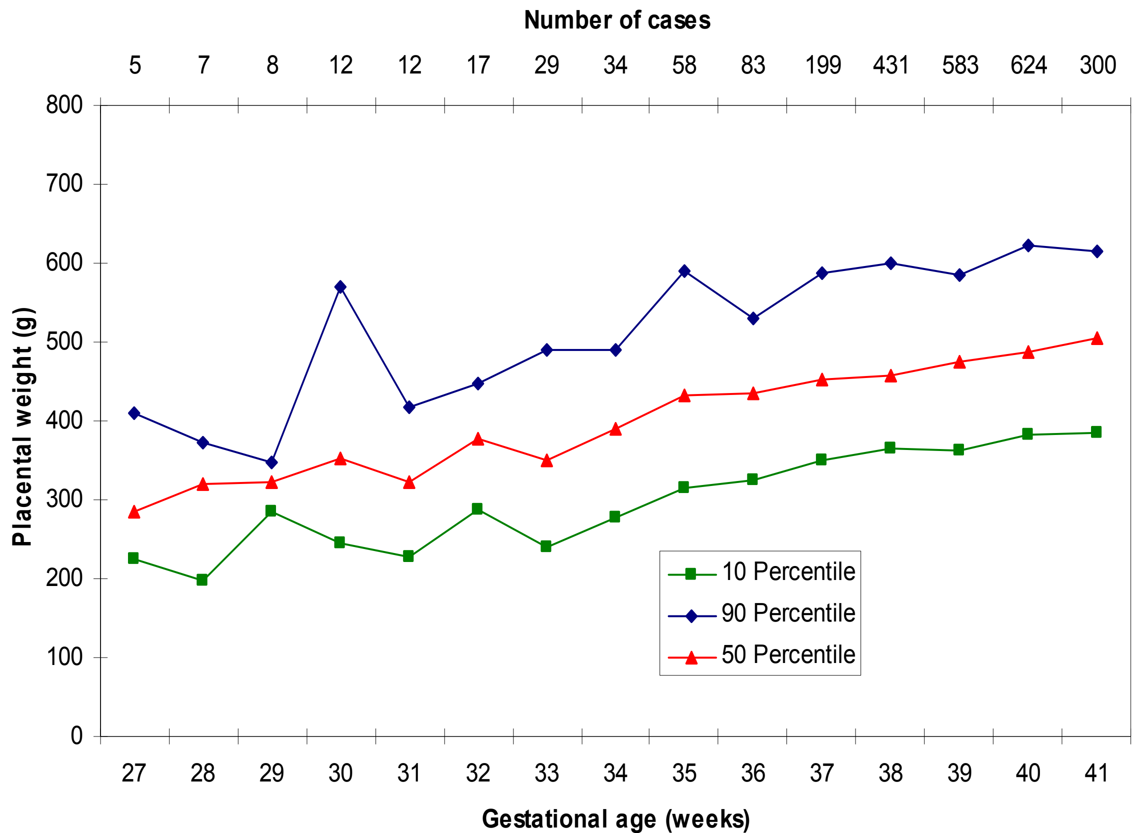


Figure 4: Placental weight changes with gestational age between the 27th and the 41st gestational week modified from data of Dy et al. (2004).

Figure 4 shows the placental weight from 2,402 placentas examined from April 1997 to April 1998 in an obstetric center in Edmonton, Alberta. The placentas were weighed after removing cord, clots and membranes and fixing the placentas in formalin.

50th percentile placental weight has an initial value of 285g in the 27th gestational week and increases to a final value of 504g in the 41st week.

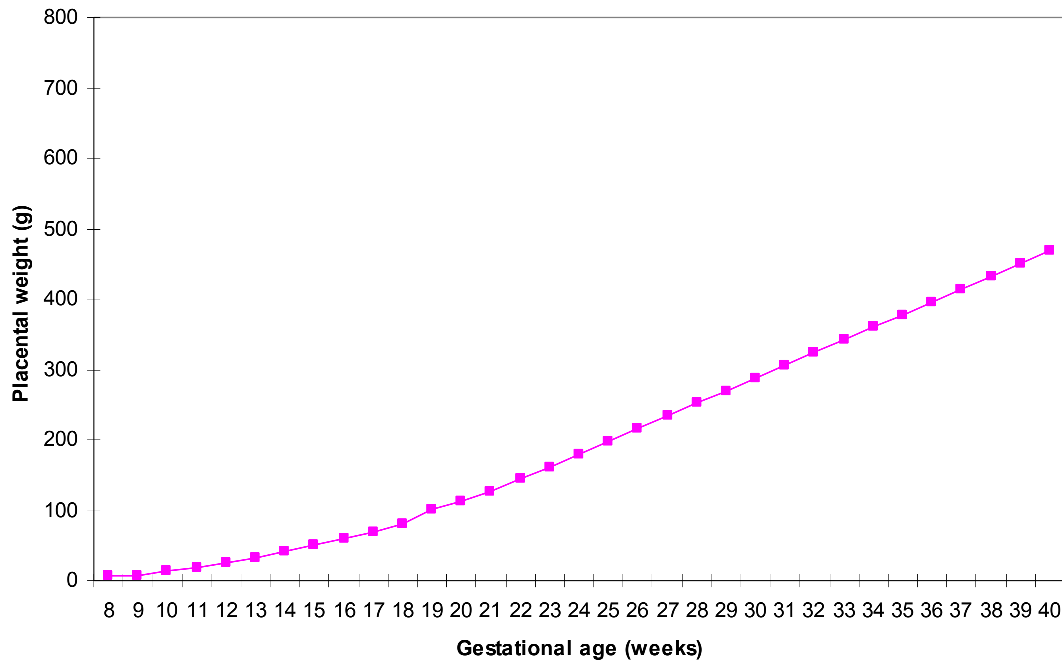


Figure 5: Placental weight change between the 8th and 40th pregnancy week modified from Benirschke at al. (2006) [data in Benirschke were taken from several other publications in which number of samples per week was not reported]

Figure 5 describes the development of the placental weight between the 8th and 40th pregnancy week. The initial weight is 6g at week 8. It increases almost linearly reaching a final weight of 470g.

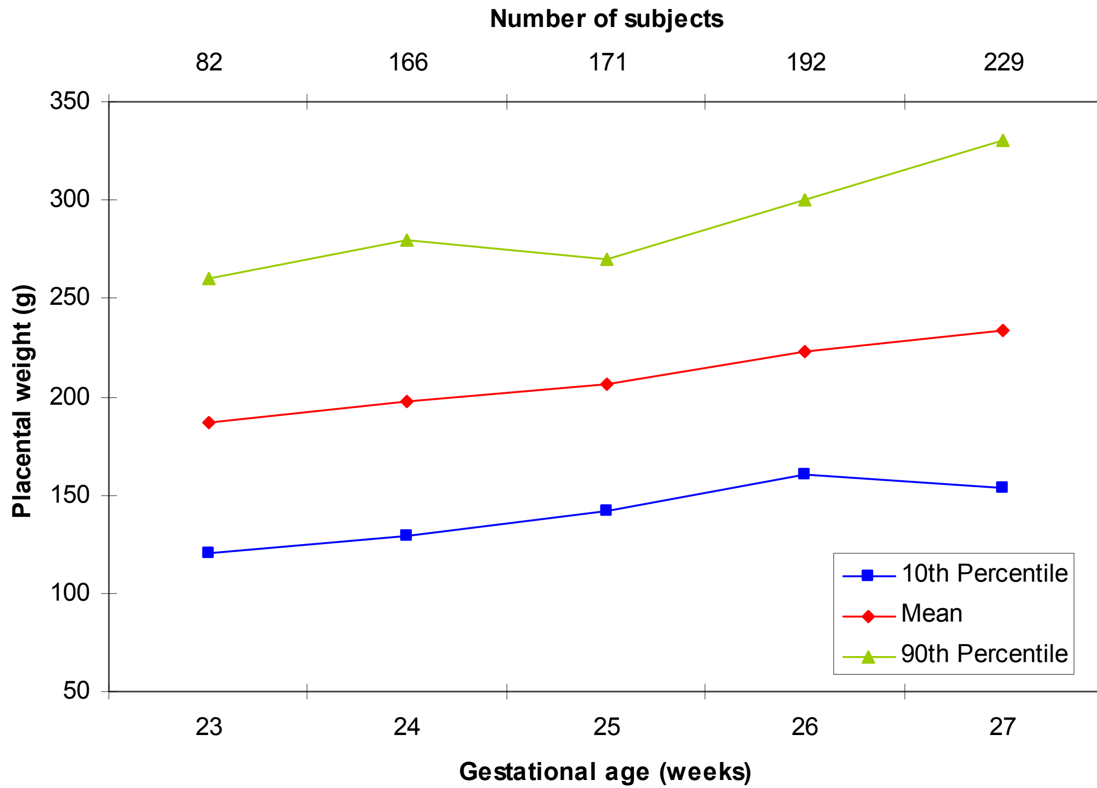


Figure 6: Placental weight development between the 23rd and the 27th pregnancy week modified from Hecht et al. (2007).

Figure 6 depicts the placental weight changes from 840 trimmed placentas between the 23rd to the 27th gestational week.

The mean placental weight shows a continuous increase from an initial value of 187g (week 23) to a final value of 234g at the 27th week.

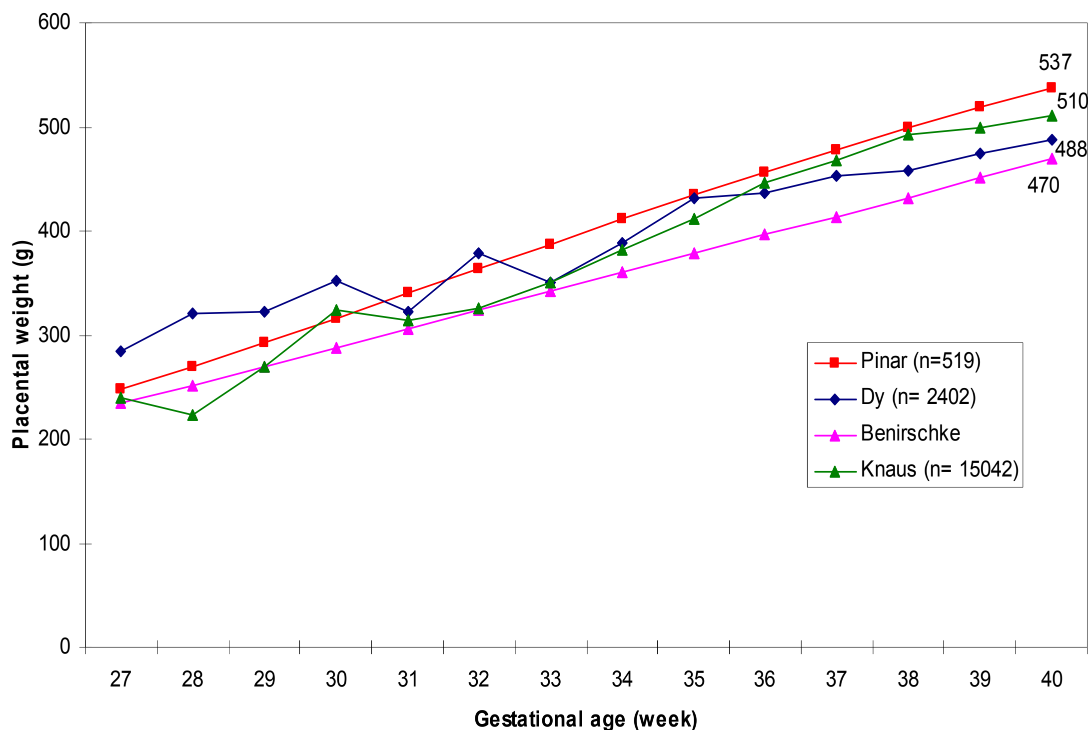


Figure 7: Comparison of weight changes of trimmed placentae. Compiled are data modified from Pinar et al. (1996), Dy et al. (2004), Benirschke et al. (2006) [data in Benirschke were taken from several other publications in which number of samples per week was not reported] and Knaus et al. (2004).

Figure 7 describes the comparison of four different curves of trimmed placental weight. All four curves show a continuous increase in the placental weight throughout pregnancy. Placenta weight curves of Benirschke et al. (2006) and Pinar et al. (1996) show a strictly linear dependency while the data of Dy et al. (2004) and Knaus et al. (2004) contain some variations. The lowest placental weights throughout pregnancy were observed by Benirschke et al. (2006). The highest mean placental weight was described by Pinar et al. (1996).

Conclusion: Placental weight increases continuously throughout pregnancy with a mean weight of 500g at term.

3.2.2 Placental weight increase per week of gestation

In order to determine placental growth rate throughout gestation the biweekly placental weight increase was used to calculate the weight increase per week (Table 2).

Table 2: Placental weight increase per week data according to Kalousek et al. (1990), Pinar et al. (1996), Dy et al. (2004), Knaus et al. (2004), Benirschke et al. (2006), Thompson et al. (2007).

Reference	Number of subjects	Week	Δ wt	wt/week
Kalousek et al. (1990)	12	8-10	27.2	13.6
	24	10-12	27.3	13.6
	29	12-14	27.2	13.6
	26	14-16	27.2	13.6
	15	16-18	27.3	13.6
Pinar et al. (1996)	15	22-24	32	16
	23	24-26	38	19
	30	26-28	43	21.5
	28	28-30	46	23
	36	30-32	48	24
	56	32-34	47	23.5
	68	34-36	46	23
	98	36-38	42	21
	255	38-40	38	19
Dy et al. (2004)	19	28-30	31.5	15.7
	29	30-32	25.5	12.7
	51	32-34	11	5.5
	117	34-36	5.5	2.7
	514	36-38	22	11
	1,055	38-40	30	15
Knaus et al. (2004)	35	22-24	26	13
	38	24-26	8	4
	63	26-28	14	7
	83	28-30	102	51
	111	30-32	2	1
	229	32-34	64	32
	698	34-36	58	29
	3,007	36-38	44	22
	6,583	38-40	17	8.5
Benirschke et al. (2006)	number of subjects is not available	8-10	7	3.5
		10-12	13	6.5
		12-14	15	7.5
		14-16	19	9.5
		16-18	20	10
		18-20	32	16
		20-22	32	16
		22-24	36	18
		24-26	36	18
		26-28	36	18
		28-30	36	18
		30-32	36	18
		32-34	36	18
		34-36	36	18
		36-38	36	18
		38-40	38	19
Thompson et al. (2007)	89	24-26	36	18
	136	26-28	49	24.5
	236	28-30	50	25
	442	30-32	61	30.5
	1,068	32-34	79	39.5
	3,371	34-36	64	32
	17,241	36-38	45	22.5
	42,479	38-40	39	19.5

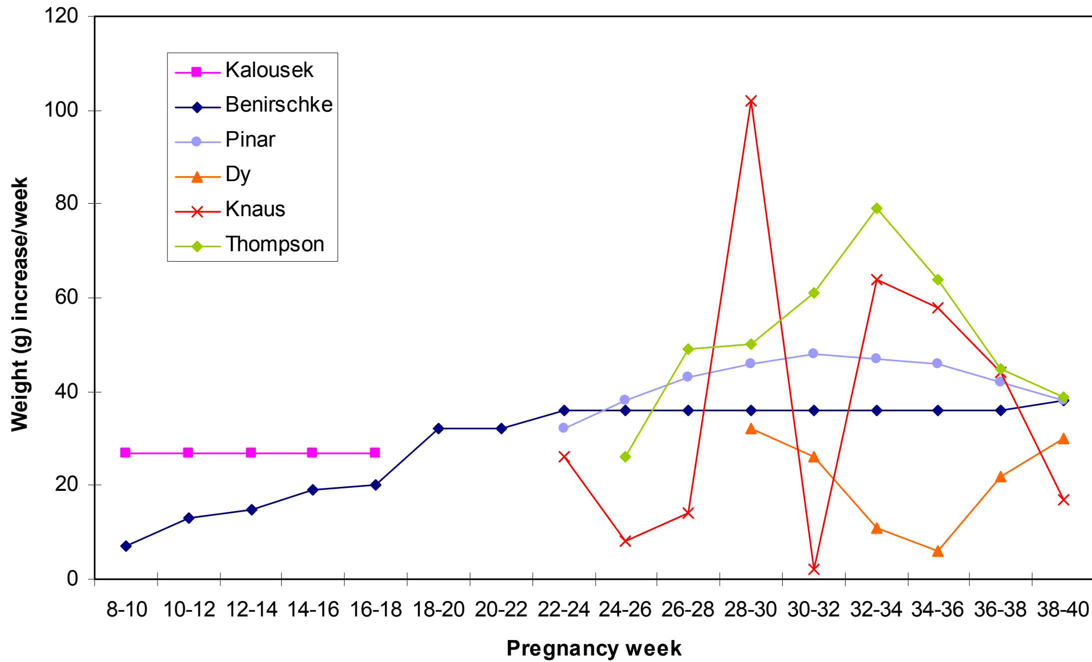


Figure 8: Comparison of biweekly placental weight increase between the 8th and the 40th gestational week. Graphic: presentation of data in table 2 modified from to Kalousek et al. (1990), Pinar et al. (1996), Dy et al. (2004), Knaus et al. (2004), Benirschke et al. (2006), Thompson et al. (2007).

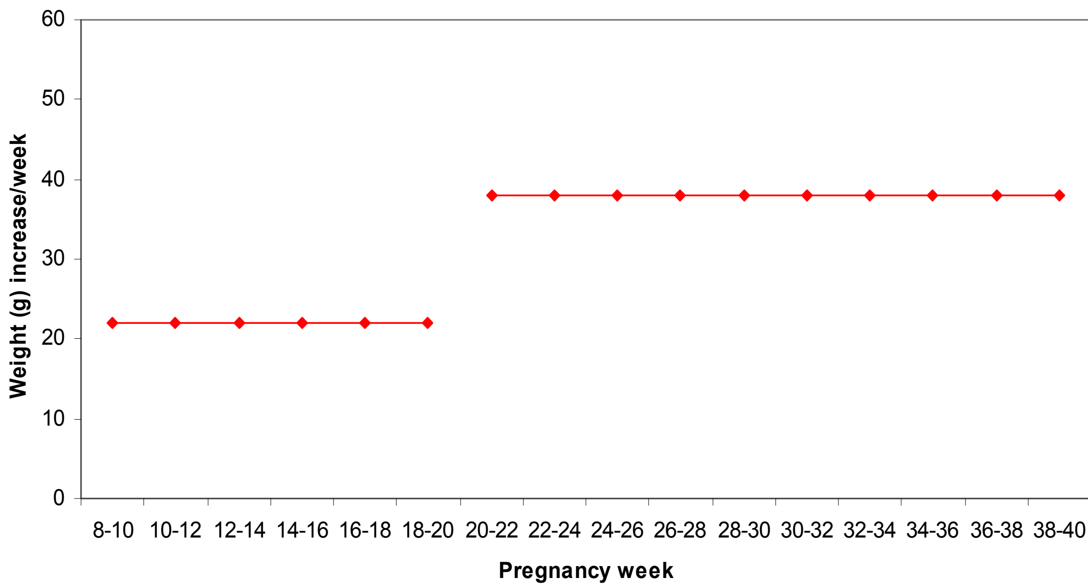


Figure 9: The calculated biweekly mean placental weight increase in the first and the second half of pregnancy.

The calculated mean biweekly placental weight increase in the first half of pregnancy is on average 22g, for the second half the biweekly weight increase is on average 38g (Figure 9).

Conclusion: A continuous placenta weight increase throughout pregnancy can be observed.

3.2.3. SECULAR TREND OF PLACENTAL WEIGHT

Infants birth weight and length increased over the last decades (Tretyak et al. 2005). Therefore the question arises if placental weight also has changed over the years.

Table 3: Overview of the change of placental weight since 1891. In order to an able comparison between untrimmed and trimmed placental weight and 16% (Lary et al. 2003) were added to the trimmed placental weight.

Year	Preparation	Placental weight (g) (40th pregnancy week)	Calculated (+16%)/ recorded untrimmed placental weight (g)	Reference
1891	u	549°	549	Benirschke et al. (2006)
1969	u	652	652	Thomson et al. (1969)
1970, 1973	t	470	545	Benirschke et al. (2006)
1977	t	450	522	Molteni et al. (1978)
1991-94	t	537	622	Pinar et al. (1996)
1997-98	t	488	566	Dy et al. (2004)
1999-02	u	690	690	Thompson et al. (2007)

u: untrimmed placental weight
t: trimmed placental weight
°data about the pregnancy week were not available

Table 3 describes the placental weight changes throughout the last decades. An placental weight increase over the last decades can be observed.

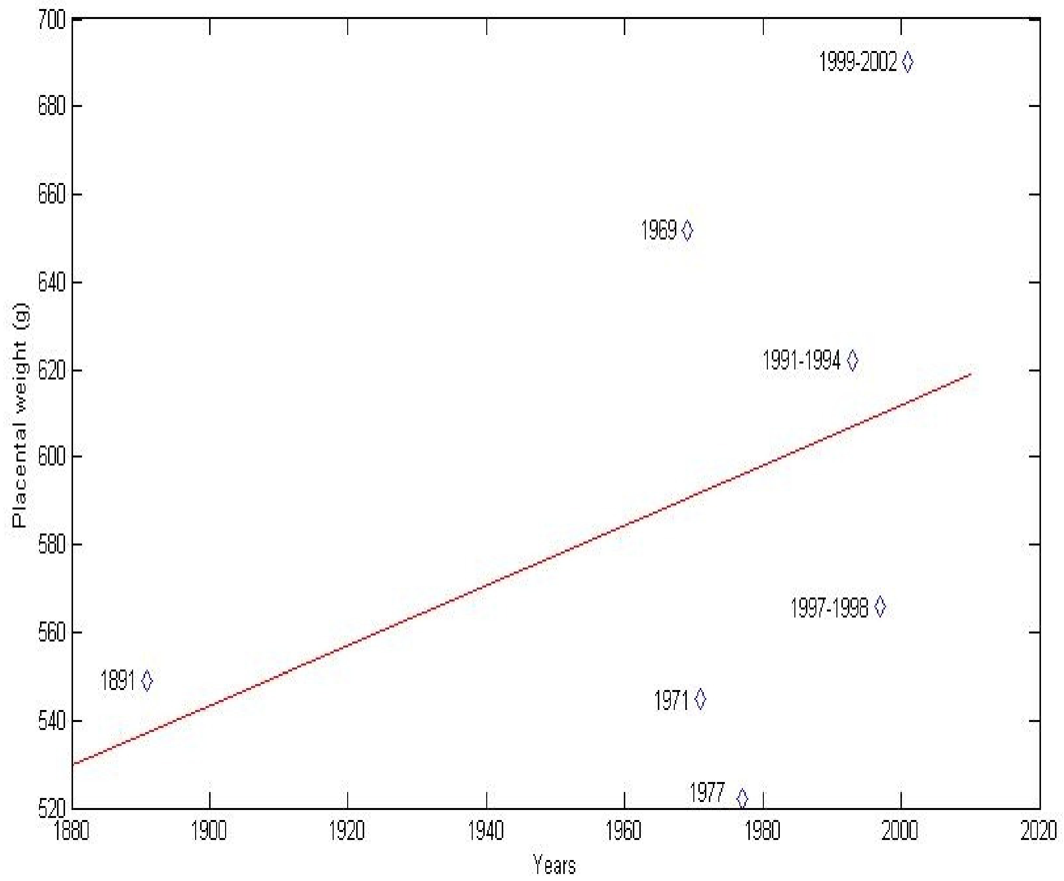


Figure 10: Overview of the untrimmed placental weight change from 1891 to 2002; data according to Benirschke et al. (2006), Thomson et al. (1969), Molteni et al. (1978), Pinar et al. (1996), Dy et al. (2004), Thompson et al. (2007).

Conclusion: An increase in average placental weight over the last decades can be observed.

3.2.4. PLACENTAL WEIGHT RELATED TO PLACENTAL DIAMETER

Apart from direct measurement of the placental weight the placental diameter has occasionally been reported as a parameter reflecting placental development.

It is closely and linearly associated with placental weight as shown in Figure 11 and Figure 12.

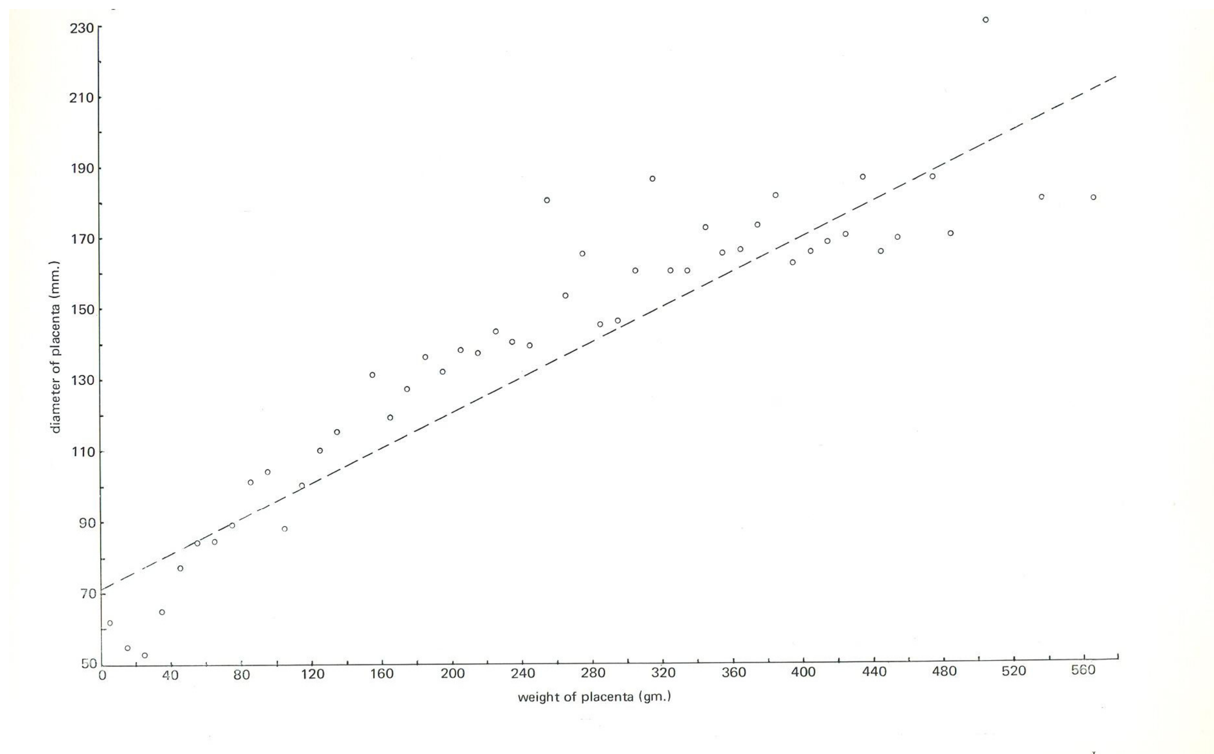


Figure 11: Relationship of the placental weight and the placental diameter adapted from (Boyd et al. 1970).

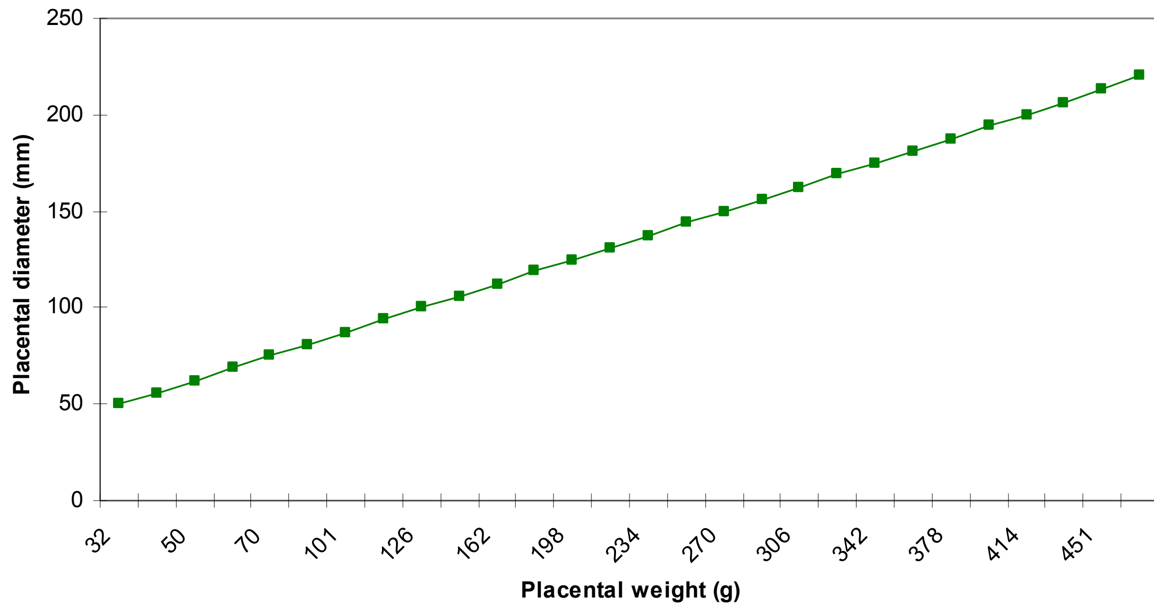


Figure 12: Placental weight and its association with the placental diameter modified from Benirschke et al. (2006).

Conclusion: Both studies show a linear association between placental weight and placental diameter.

3.3. Gender specific placental weight

Fetal weight is gender dependent. Male birth weight at 40 weeks is on average 119g higher than female birth weight (Thompson et al. 2007). Hence the question arises if the gender of the fetus also has an influence on placental weight.

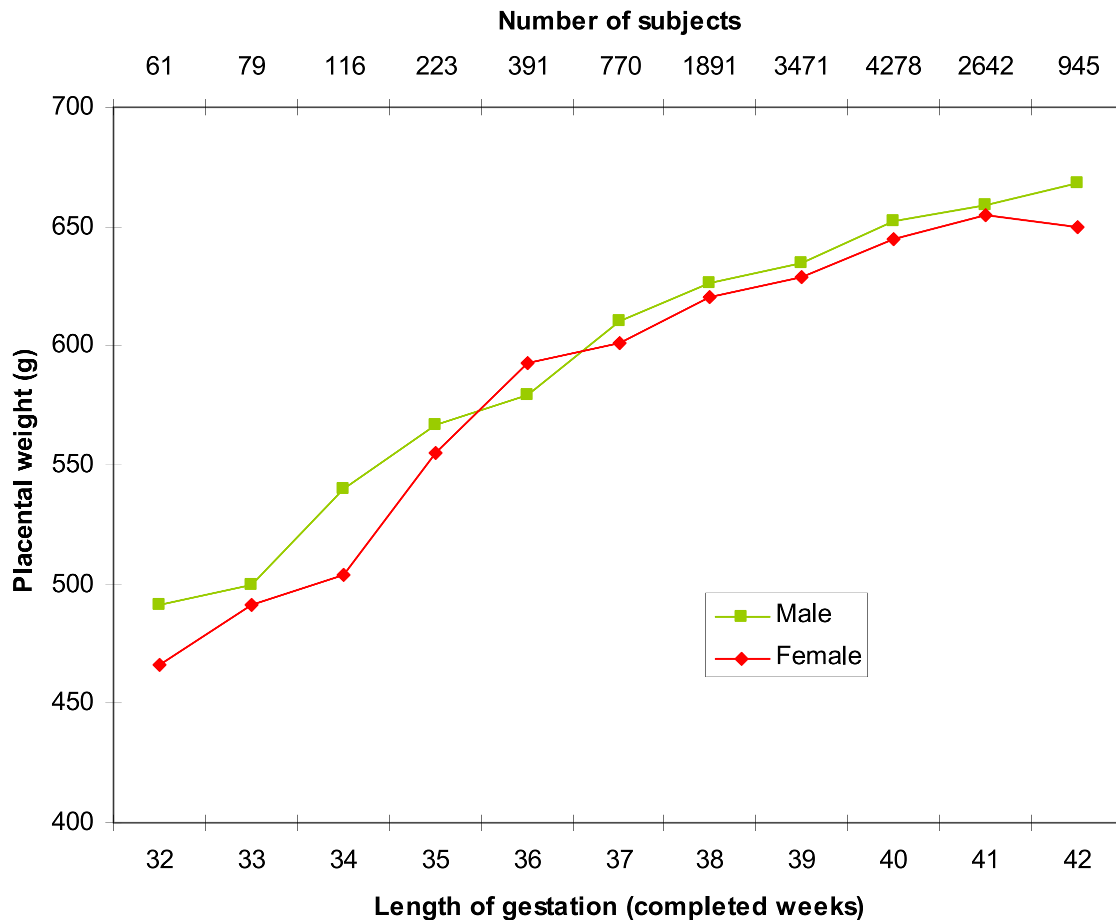


Figure 13: Comparison of sex specific untrimmed placental weights between the 32nd and the 42nd pregnancy week modified from Thomson et al. (1969).

Thomson et al. (1969) compiled a sex specific list of the mean untrimmed placental weights during the years 1948-64 in the city of Aberdeen.

Figure 13 describes the change of the placental weight of 7687 male and 7180 female placentas from first pregnancies between the 32nd and the 42nd gestational week.

During the whole period the placental weight of females is lower compared to males except for the 36th gestational week. "The present data show that the male placenta is slightly smaller than the female, not absolutely, but relative to fetal weight. In other

words, the placenta is able to support the greater growth of male fetus without a commensurate increase in size" (Thomson et al. 1969).

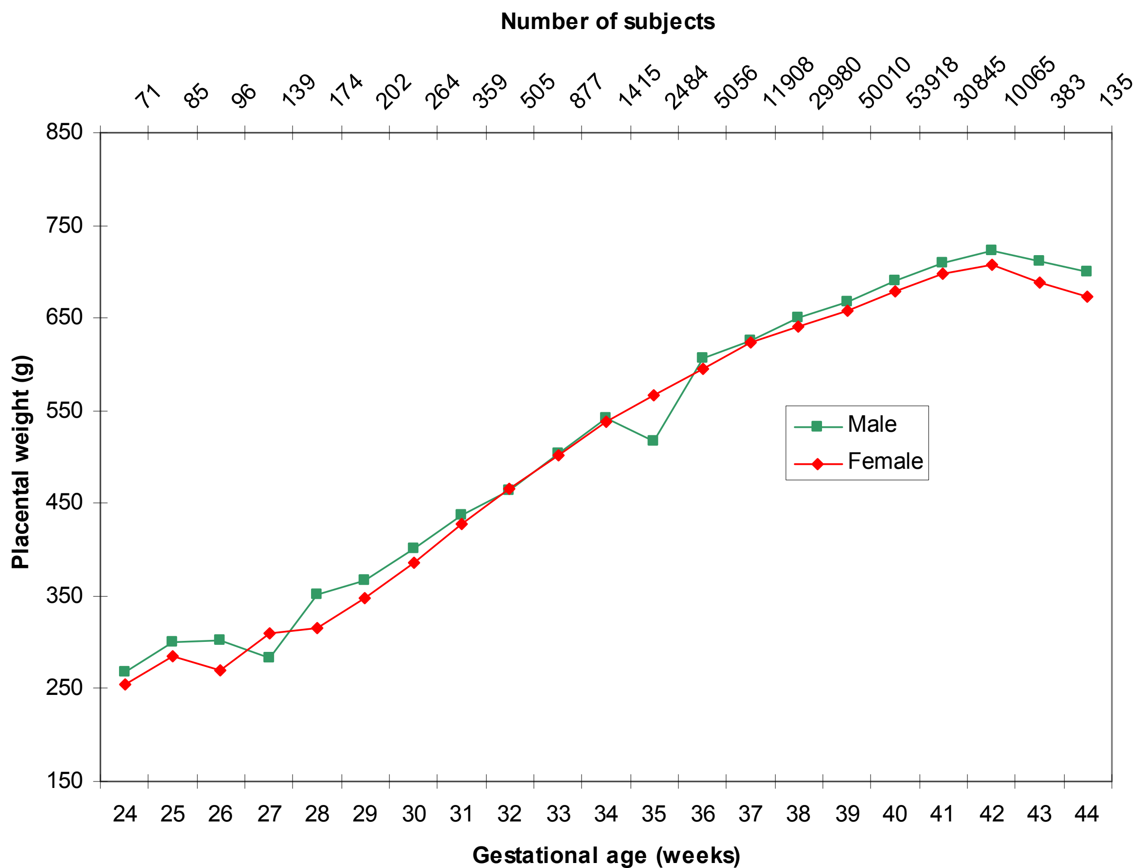


Figure 14: Comparison of untrimmed sex specific placenta weights between the 24th and the 44th gestational week modified from Thompson et al. (2007).

Thompson et al. (2007) examined the sex-weight dependency of 198.971 placenta samples collected in the years 1999-2001 in Norway. The results are depicted in the figure above.

Figure 14 describes the mean female and male placental weights between the 24th and the 44th gestational week. "The placental weights of male were slightly higher than those of female infants, but the size of the difference was not of the magnitude seen in birth weight, with differences in the median (50th percentile) of the male and female curves amounting to 20g at most" (Thompson et al. 2007). The placental weight decrease after the 42nd gestational week may be explained by a decrease of examined placentas.

However Charles H. Hendricks (1964) reported that in his study the male placenta tended to be larger than the female placenta, the difference being 2.32% at 40 weeks (Hendricks 1964).

Another opinion is that the placental weights of boys and girls are the same throughout pregnancy (Bleker et al. 2006). They concluded that male infants being heavier because they demand more from their placentas as compared to girls.

Furthermore female infants had significantly lower birth weights than male infant but only a small trend to lower placental weights (Williams et al. 1997).

Table 4: Comparison of male and female placental weight and their weight difference in %. Data, according to Hendricks (1964), Thomson et al. (1969), Thompson et al. (2007).

Male placental weight (g) (40th pregnancy week)	**Female placental weight (g)** (40th pregnancy week)	**Placental weight difference (%)**	**Reference**
n.A.	n.A.	2.3	Hendricks (1964)
652	645	1	Thomson et al. (1969)
690	678	1.7	Thompson et al. (2007)
		1.7	Average

n.A.: data not available

Conclusion: Placental weight of male infants is typically about 1.7% higher than of females. However the weight difference is not similar in magnitude to the average birth weight difference which is 3%.

3.4. PLACENTAL WEIGHT DEPENDING ON PARITY

Children from multiparous women are heavier than children from primiparous women, the mean difference at 40 weeks being 200g. Similar observations were made for the placenta. The placentas of multiparous women are heavier than those in primiparous women. This difference is manifest already from 25 weeks onwards (Bleker et al. 2006).
Naeye (1987) described low parity as a factor contributing to placental undergrowth and Thomson et al. (1969) who reported that placental weight tends to be greater in multiparous women than women pregnant first.
In addition the placental weight of the fetus born to the multipara was compared to those fetuses born to the primigravida, concluding that the placental weight difference at 40 weeks is 2.50% respectively, in favor of the multipara (Hendricks 1964).
Moreover, the Figure 15 below presents the mean placental weights in relation to the number of pregnancies. The mean placental weight of the first baby was 428g while placental weight in a second pregnancy 440g. In case of two previous pregnancies the weight was 440g compared to 3-9 previous births where a mean weight of 446g was described (Salafia et al. 2008).

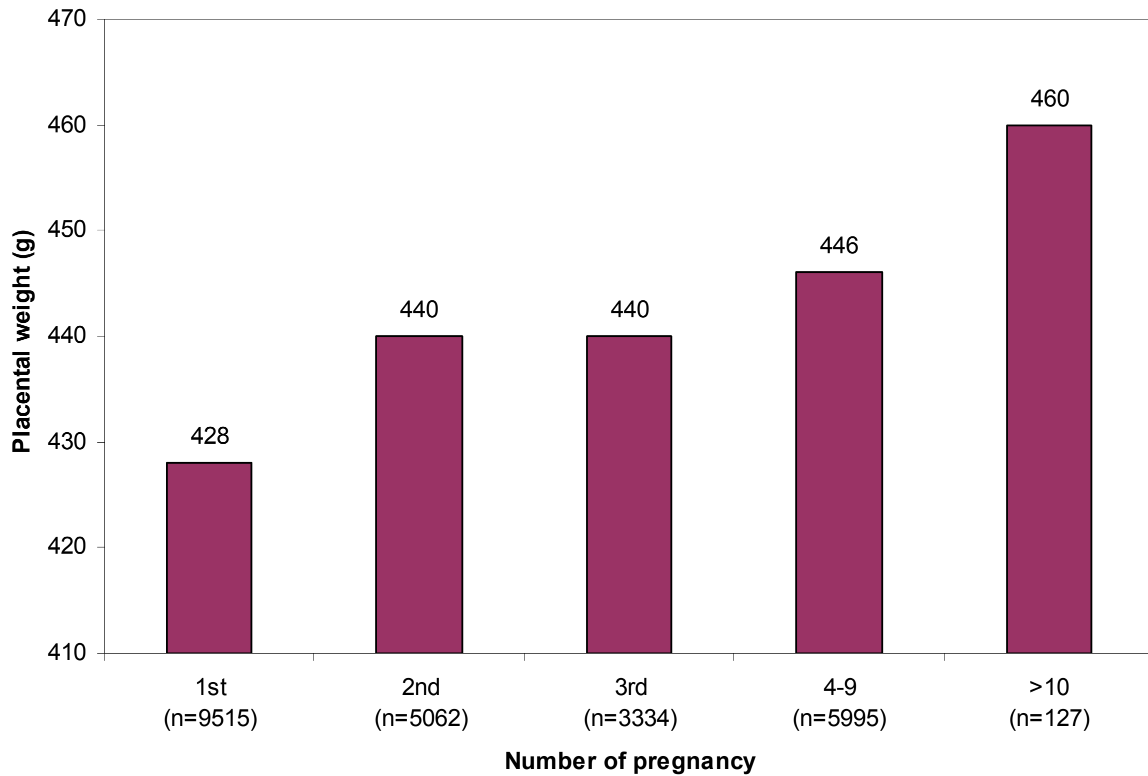


Figure 15: Placental weights depending on parity delivered between the 34th-42nd gestational weeks modified from Salafia et al. (2008).

This study is based on trimmed weight of 24,061 placentas delivered from 34th-42nd gestational week (Salafia et al. 2008)
A similar table presenting the placental weights related to the numbers of pregnancies was created by Benirschke et al. (2006) (Figure 16) and it also took into account the sex of the fetus.

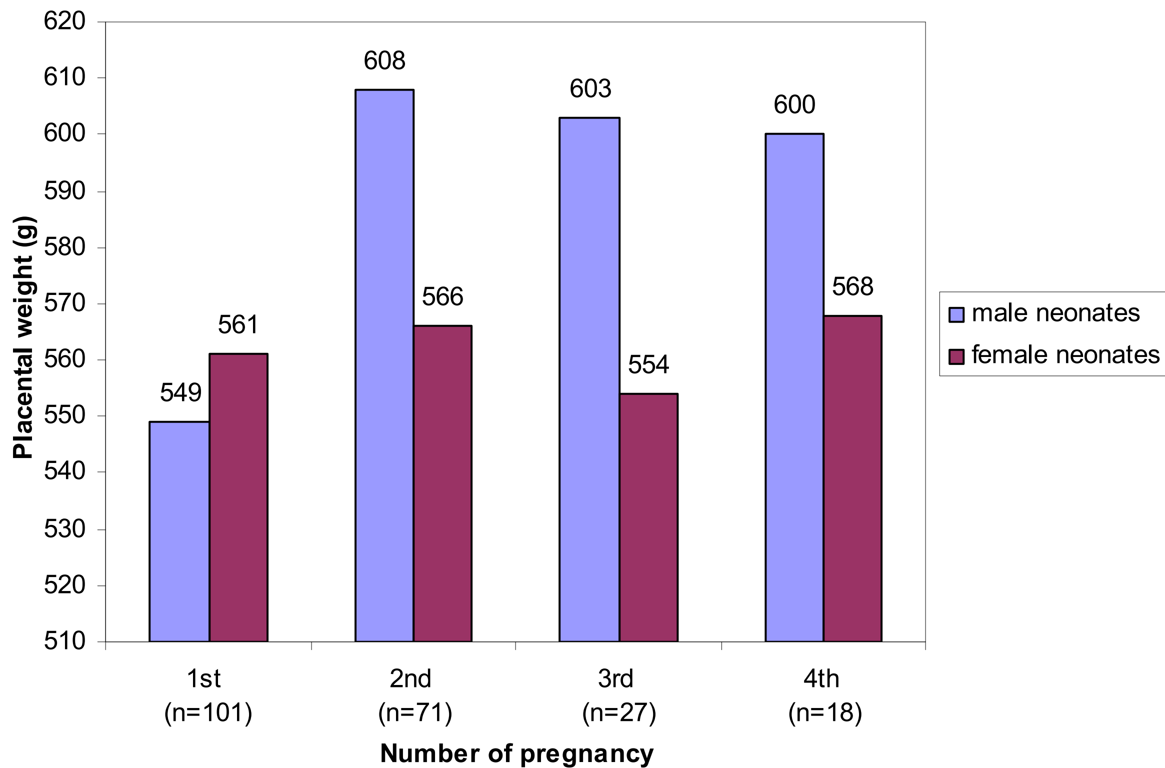
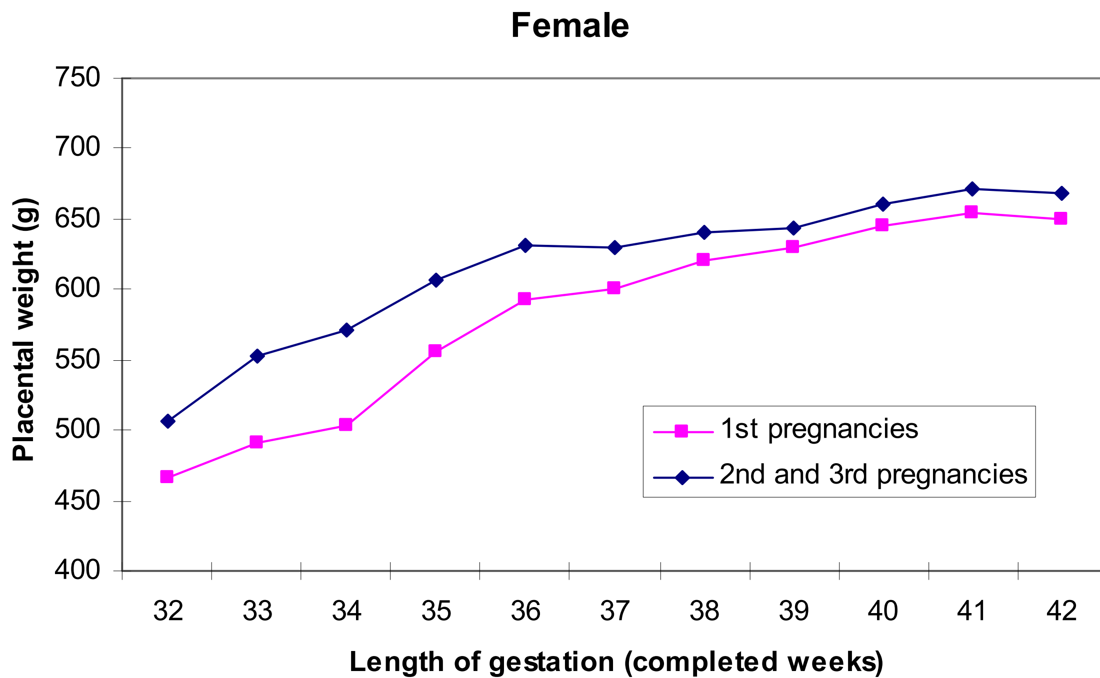


Figure 16: Sex specific placental weights depending on parity modified from Benirschke et al. (2006) [data in Benirschke were taken from Lips 1891].

Male placental weights show the lowest values at first pregnancies. Placental weights of second pregnancies increase about 50g while the weights in the second, the third and the fourth pregnancies are almost the same. In contrast female placental weights do not show these weight differences with increasing number of pregnancy (Figure 16).

Although these studies show an influence of parity on placental weigh, another study did not find a significant difference in mean placenta weight and mean pregnancy age at parturition between several parity groups. It was concluded that other factors than parity influence the growth and weight of the placenta (Lolis et al. 1998).



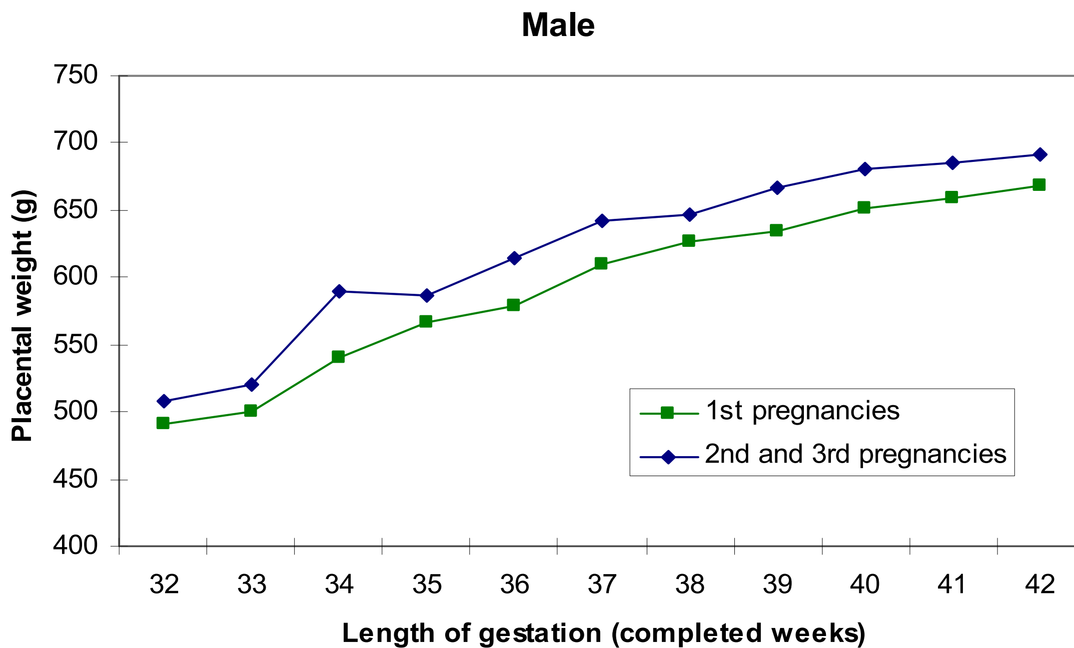


Figure 17: Untrimmed placental weights depending on parity and gender of the neonate delivered between the 32nd and the 42nd gestational week modified from Thomson et al. (1969).

Figure 17 describes the placental weight changes in female and male offspring related to the parity of untrimmed placentas between the 32nd and the 42nd gestational week.

The female and male placental weight curve of second and third pregnancies was consistently higher compared to first pregnancies.

Conclusion: A positive correlation between the placental weight and the number of pregnancies is described. However, the most significant placental weight difference can be observed between the first and second pregnancy.

3.5. PLACENTAL WEIGHT AND BIRTH WEIGHT

The initial growth of the placenta is much more rapid compared with the growth of the fetus. The fetus needs nearly half of the pregnancy duration to achieve the first 10% of its ultimate weight at term. Observations show that the fetal growth follows a sigmoid curve. After the 30th gestational week fetal weight rises rapidly to a maximum increase of 34g per day. Around the 40th week the weight gain decreases to 18g per day. "…while the fetus achieves 90% of its final weight about 17 days before term, the placenta achieves 90% of its final weight approximately 22 days before term" (Hendricks 1964).
There is a linear growth relationship between placental and fetal characteristics allowing the assumption of linearity in the last five month of gestation (Hamilton et al. 1973).
Moreover it was described that for each gram increase in placental weight, birth weight increased by 1.98g (Sanin et al. 2001).
Thompson et al. (2007) published percentile curves of placental weight and birth weight with 198,971 samples. They observed that the placental weight percentile curve is much flatter than that of the birth weight. The birth weight curves show a relatively steep increase and around the 24th gestational week a time of maximal growth of the fetus. The weight gain of the fetus starts to level off at approximately term.
However, it was also reported that the placental weight increases linearly with the weight of the fetus, these observation are based on 50 human trimmed placentas (Winick et al. 1967).
Another study focused on the final weeks of gestation. The fetus gained weight faster than the placenta in this period of pregnancy. However, the relative fetal weight gain per week falls from about 25% at 32 weeks of gestation to about 19% at term. "At any given placental weight, mean birth weights increases with duration of gestation and are about 0.5 kg greater at term than at 35 weeks" (Thomson et al. 1969).
For example babies which are born at 35 weeks with a weight of 2,500g have placentas of about the same average weight as babies with the same weight born at term (Thomson et al. 1969).
Also Bleker et al. (2006) described that the fetal growth decelerates after 38th weeks.
They conclude that the cause of this deceleration must be due to a limitation of the placenta and the mother.

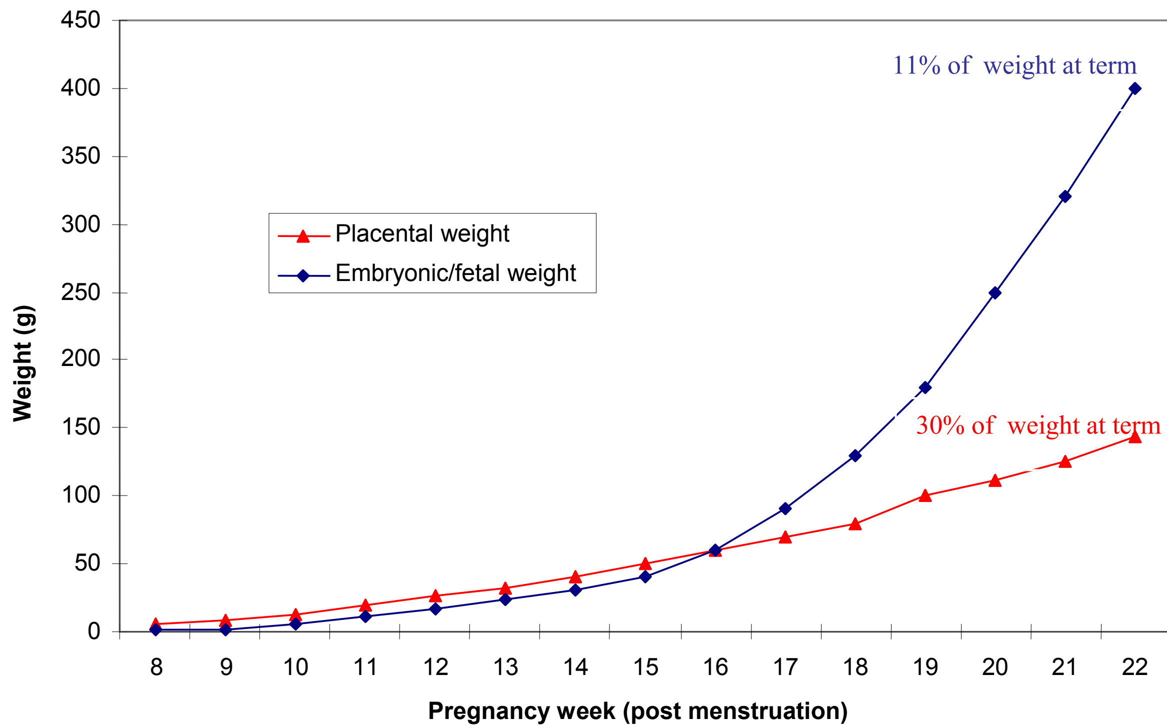


Figure 18: Placental weight compared to embryonic/fetal weight between the 8th and the 22nd pregnancy week modified from Benirschke et al. (2006) [data in Benirschke were taken from several other publications in which number of samples per week was not reported].

Figure 18 describes the association of the placental and fetal gain between the 8th and the 22nd week of pregnancy.

The placental weight at the 8th pregnancy week is 6g and increases continuously to a weight of 144g at the 22nd week.

The fetal weight curve starts with a weight of 1.1g at the 8th week and is much flatter in the first weeks of gestation until the 16th week where the fetal weight curve increases precipitously to a weight of 400g at the 22nd week.

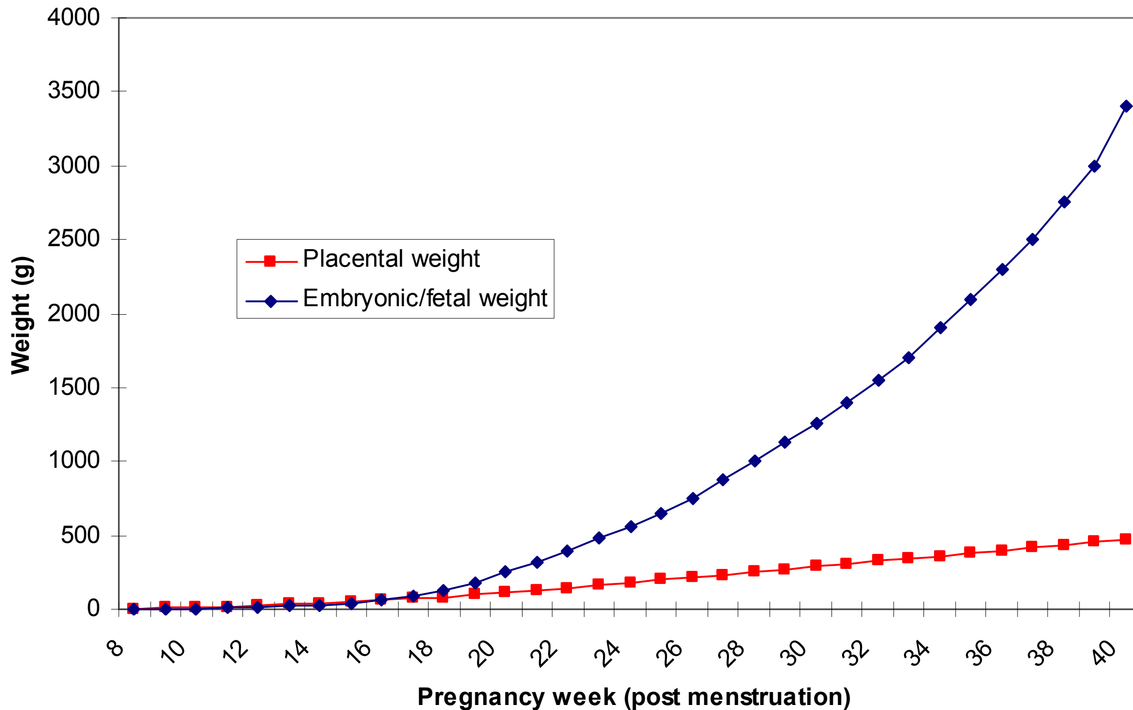


Figure 19: Placental weight compared to birth weight between the 8th and the 40th gestational week modified from Benirschke et al. (2006) [data in Benirschke were taken from several other publications in which number of samples per week was not reported].

Figure 19 depicts the relation between the placental and the fetal weight during the 8th and the 40th gestational week. Hence it extends
until term.

The placental weight curve shows an initial weight of 6g and rises continuously to the final weight of 470g at the 40th week.

The fetal weight curve starts at a weight of 1.1g and inclines marginally until the 16th gestational week. Thereafter the weight gain increases steeply to the final weight of 3,400g.

These two curves run almost identically close to one another until the 16th gestational week. Subsequently the fetal weight gain increases much steeper than before. The placental weight curve increases continuously, but much slower compared to the fetal weight curve until the 40th week.

Conclusion: Placental weight gain, in the first weeks of pregnancy, is much higher compared to the fetal weight gain. However, after the 16th gestational week the fetal weight gain increases steeply.

3.5.1. FETAL-PLACENTAL WEIGHT RATIO

The fetal-placental weight ratio describes the fetal weight divided by the placental weight. In biological term it represents the amount of fetal tissue (in g) sustained by 1g placental tissue.

Lurie et al. (1999) reported that earlier work described a fetal-placental weight ratio of approximately 7 at term. Their observations are based on 394 consecutive singleton, near-term, deliveries relating to the placenta weight of trimmed placentas. They described a fetal-placental weight ratio of 5.6±0.96. The fetal-placental weight ratio was associated with maternal age at delivery and fetal weight. Low fetal-placental weight ratio was associated with teenage women, early near-term gestational age and low fetal weight. A progressive increase was related with gestational age and birth weight distribution. “This study confirms an earlier observation that fetal-placental weight ratio increases in late gestation with the growth of fetus disproportionate to the growth of the placenta” (Lurie et al. 1999).

Likewise a study with 11,000 placentas showed a mean fetal- placental weight ratio of 5.5 at term. However the placental weights were determined from placentas plus cords and membranes i.e. from untrimmed placentas (Hendriks 1964).

On the contrary a mean term infants fetal-placental weight ratio of 7.9 was described. The explanation for their observation was that they exercises special care to drain the blood from the placenta vessels. Moreover a fetal-placental weight ratio less than 7.0 at 17 of 23 preterm infants was described. In contrast ratios greater than 7.0 were calculated in 19 of 30 intrauterine growth-retarded infants (Younoszai et al. 1969).

Molteni et al. (1978) also observed a fetal-placental weight ratio of about 7.6. They reported that the fetal-placental weight ratio increases with increasing gestational age independent of the infants size.

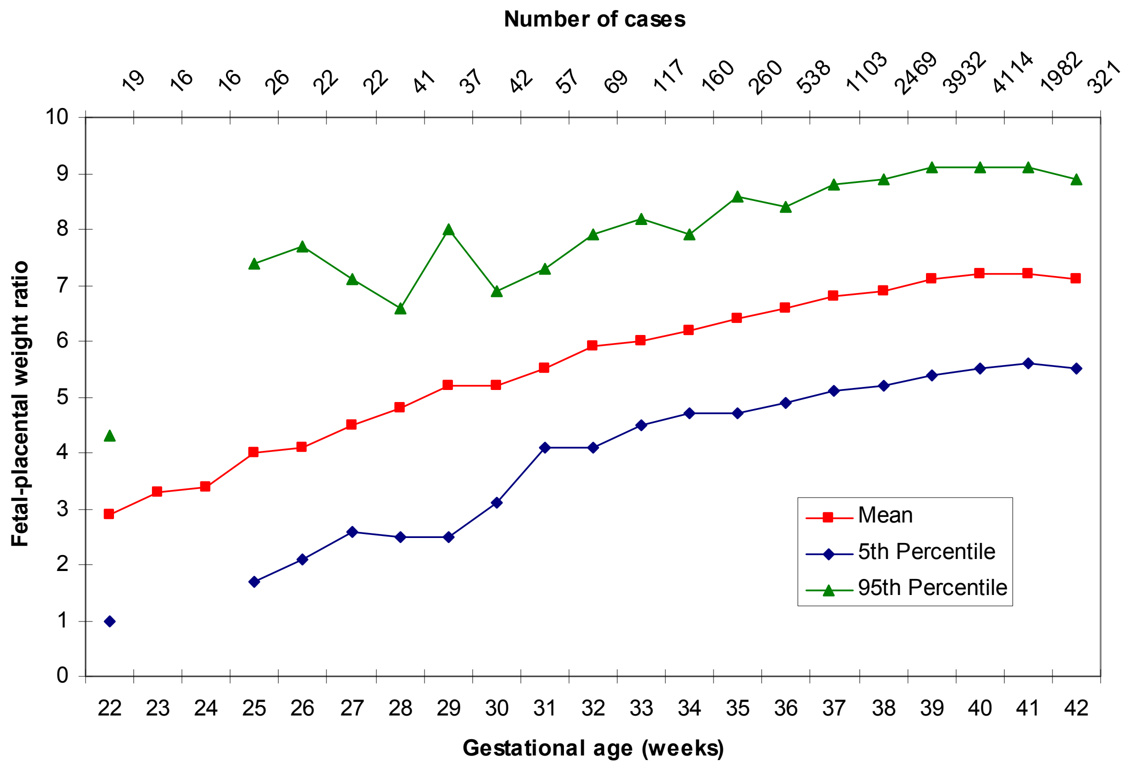


Figure 20: Fetal-placental weight ratio between the 22nd and 42nd gestational week modified from Knaus et al. (2004).

Figure 20 describes the change of the fetal-placental weight ratio between the 22nd and 42nd gestational week. It increases from 2.9 at week 22 to 7.1 at week 40.

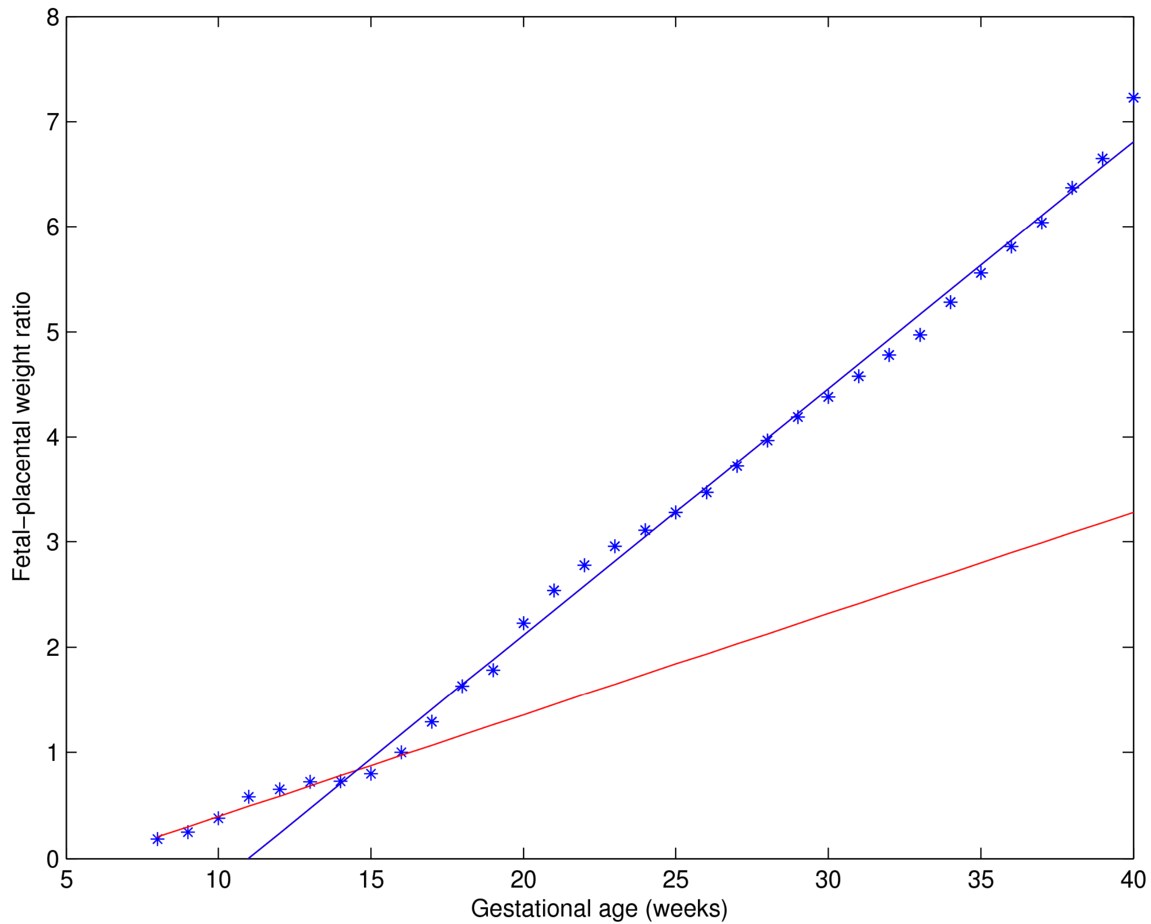


Figure 21: Fetal-placental weight ratio modified from Benirschke et al. (2006) [data in Benirschke were taken from several other publications].

Figure 21 presents a description of the fetal placental weight ratio between the 8th and the 40th pregnancy week. The curve starts with an initial ratio of 0.18 at the 8th week and increases approximately linear to a final ratio of 7.23. From week 15 onward the initial slope becomes steeper indicating that the fetal growth rate exceeds that of the placenta.

Conclusion: In the literature fetal-placental weight ratio values between 5.5 and 7.9 can be found. An important factor influencing the ratio is the placental preparation. The mean fetal-placental weight ratio in case of trimmed placentas is about 7 at term.

A few authors developed formulas to calculate the birth weight of the fetus according to the placental weight.

Dombrowski et al. (1994) reported that birth weights should be proportional to the square of placental weights. "….we hypothesized that birth weight should be proportional to placental weights raised to the 2nd power, rather than the 1.5th power" (Dombrowski et al. 1994).

Dombrowski:

$$W=0.0071\times P^2$$

W= birth weight; P= placental weight unlike Aherne`s:

Aherne:

$$W= 0.1861\times P1.5.$$

However, they pointed out that this formula may not apply to all ethnicities and nationalities and that it was very sensitive to placental preparation (Dombrowski et al. 1994).

Exactly these limitations were criticized by Sanin et al. (2001) who reported that the placental volume in the second trimester was a good predictor of birth weight. Furthermore they described that lesions in the placenta could change the development of the fetus or could determine a delay in the intrauterine growth. Throughout their work they studied 285 mothers. "It shows that for each gram increase in placental weight, birth weight is increased by 1.98g (SE=0.25, $p<0.001$) and that this relation is not linear since the quadratic term is significant" (Sanin et al. 2001).

Another research group observed 2507 singleton pregnancies delivered after 37 completed weeks. The placentas were weighed wet without trimming the membranes or cord.

"The 90% confidence intervals for the individual predicted values showed that in general infants with a higher than average placental weight to birth weight ratio had birth weights and placental weights which spanned the range for typical births" (Williams et al. 1997).

Gestational age at delivery, Asian parentage, female infant, maternal anaemia, a higher maternal weight and body mass index at booking, lower socioeconomic score, and

increasing number of cigarettes smoked daily during pregnancy were aspects that were significantly and positively connected with the placental to birth weight ratio. However, they did not find a consistent association between the placental to birth weight ratio and measures of newborn size (Williams et al. 1997).

Conclusion: Several authors tried to predict birth weight based on placental weight, but due to the large amount of different influencing factors no general conclusion could be found. Therefore, the formulas reported by different authors vary considerably.

3.5.2. PLACENTAL WEIGHT IN RELATION TO BIRTH WEIGHT CATEGORY

Related to placental weight dependent on fetal weight is the question if the placental weight is associated with the birth weight category of the infant.

Molteni et al. (1978) divided the study population in three infant groups: SGA (Small for gestational age), AGA (Appropriate for gestational age) and LGA (Large for gestational age) infants (the exact value of the percentile for group assignment is not given by the author). It is described that the placental weight increased until term just in case of the placentas of AGA (Appropriate for gestational age) and LGA (Large for gestational age) infants. Moreover they described that the placentas of LGA infants were larger than placentas of AGA infants at all gestational ages. In contrast the placentas of SGA (Small for gestational age) achieve the maximum weight at about the 36 week thereafter the placental weight increase is negligible. The placental weight of SGA was significantly below to the AGA infant group especially from the 27th to the 43rd gestational week. Moreover they compared the fetal-to-placental weight ratio between the three groups and described a ratio increasing throughout gestation independent of the growth group of the infant. In addition they related the fetal-placental weight ratio to the Apgar score of the infant after delivery and found "….a statistically significant increase in depressed infants (Apgar<6) when the fetal-placental weight ratio was greater than 10, regardless of the growth characteristics of the infant. This observation suggests that placental function is precariously balanced in those infants, who must receive their supply of oxygen and other nutrients from relatively little placental tissue" (Molteni et al. 1978).

Table 5: Placental weight changes associated with the infants size according to Molteni et al. (1978).

	SGA	AGA	LGA
Fetal weight (g)	2415	3297	3980
Placental weight (g)	309	437	547
Fetal/placental weight	7.7	7.9	7.4

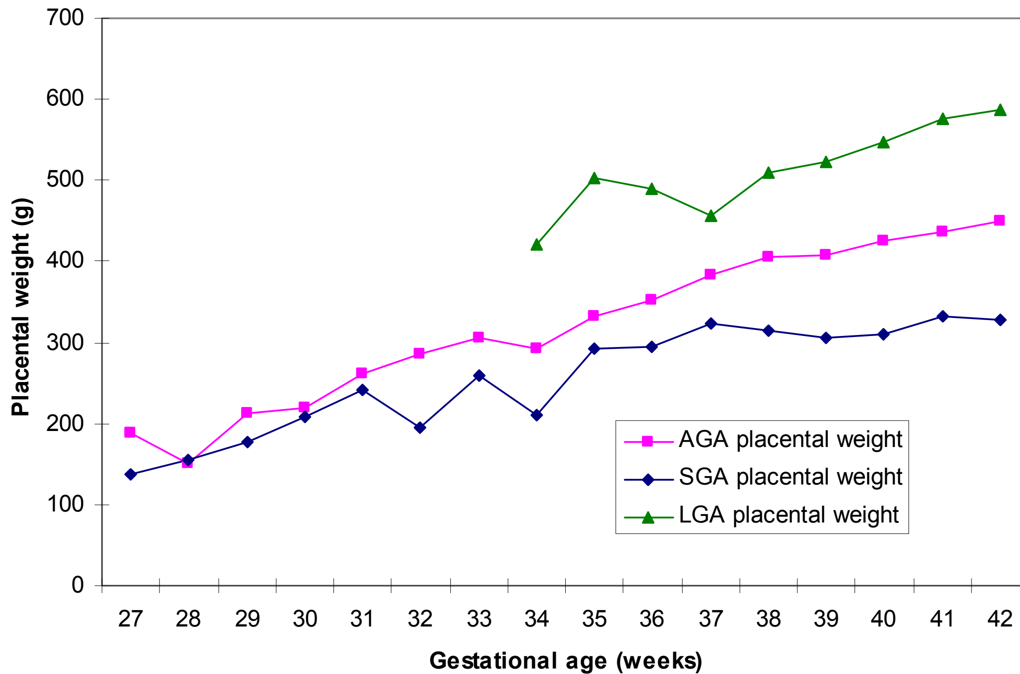


Figure 22: Placental weight development associated with the infants size according to Molteni et al. (1978).

Also Bortolus et al. (1998) divided the study population in women with SGA (birth weight < 10th percentile), AGA (birth weight ≥10th and ≤90th percentile) or LGA (birth weight > 90th percentile) infants and distinguished between uncomplicated und complicated pregnancies. They described that the mean placental weight of the SGA group was at term 29% lower compared to the LGA group. While the placenta ratio (placenta/birth weight ratio) increased from the LGA to the SGA infant group with no difference between the uncomplicated pregnancies and pregnancies complicated by IUGR (intrauterine growth retardation) or PIH (pregnancy induced hypertension).
"The results of this analysis show in groups of uncomplicated and complicated pregnancies at different risk of intrauterine growth retardation that placental/birth weight ratio increases with decreasing birth weight" (Bortolus et al. 1998).

Contrary to the studies mentioned above, Heinonen et al. (2001) collected data from 15,047 AGA (birth weight ≥10th and ≤90th percentile) and 1569 SGA (birth weight < 10th percentile) infants. They observed 24% lower placental and birth weights of SGA compared to AGA infants. The placental weight to birth weight ratio was similar SGA and AGA. It was observed that the placental weight to birth weight ratio decreased, i.e. the fetal to placental weight ratio increased, with gestational age and with increasing fetal

weight in both groups. Moreover the placental to birth weight ratio should be compared on a birth weight basis independent from gestational age. With this comparison it was demonstrated that SGA infants show lower placental weight ratios than AGA infants of the same birth weight (Heinonen et al. 2001).

Conclusion: Significantly higher placental weights of LGA infants compared to SGA infants are described.

3.6. PLACENTAL WEIGHT IN TWIN AND TRIPLET PREGNANCIES

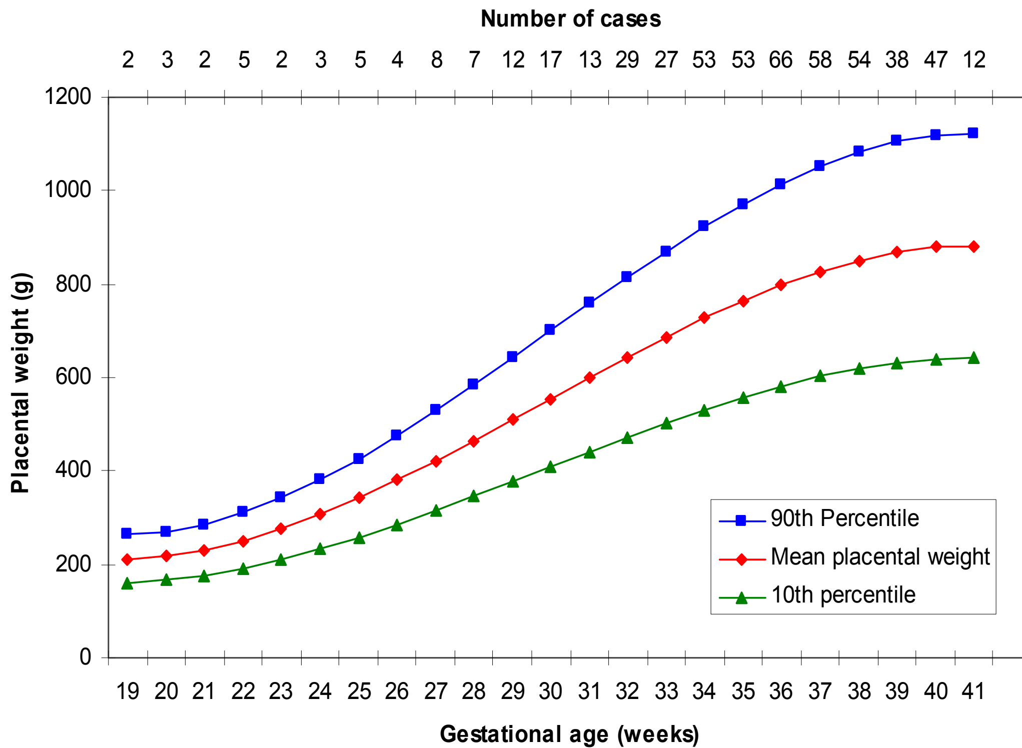


Figure 23: Trimmed twin placental weight between the 19th and the 41st gestational week modified from Pinar et al. (1996).

Figure 23 shows the placental weight of 514 twin placentas which were examined between January 1991 and September 1994 with a gestational age of between 19 to 41 weeks. The placentas were weighed in a fresh unfixed state after removing the membranes, the umbilical cord and excessive blood.

392 of the 514 placentas were diamnionic-dichorionic, 114 diamnionic-monochorionic, and 8 monoamnionic-monochorionic.

Placental weight in these twin placentas increases up to the 37th week thereafter it levels off.

The mean placental weight (red) at week 19 is 212g in the 19th week and increases to the final weight of 882g in the 41st week (Pinar et al. 1996).

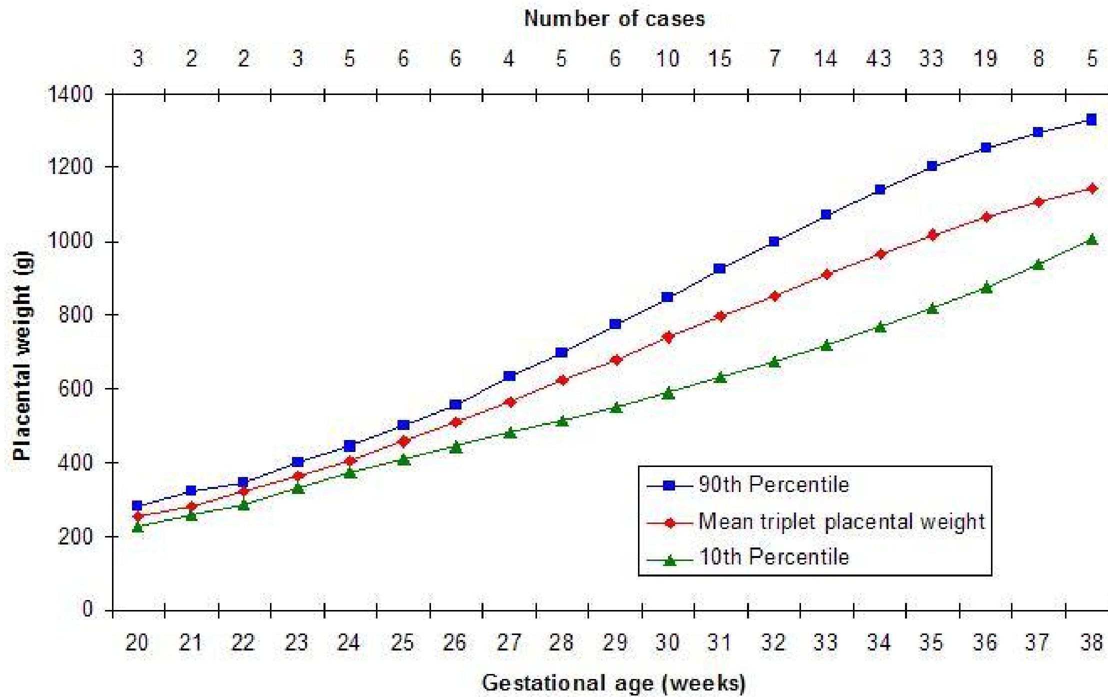


Figure 24: Trimmed triplet placental weight between the 20th and the 38th pregnancy week modified from Pinar et al. (2002).

Figure 24 describes the placental weight of 196 triplet placentas with gestational ages between 20 weeks to 38 weeks which were weighed fresh after removing membranes, umbilical cords and excessive blood. In case of separate discs in placentas with multiple discs the separate ones were weighed separately, however, only total weight was included in this study.

The mean triplet placental weight shows an almost linear increase with a weight of 253g in the 20th week and a final weight of 1147g in the 38th week (Pinar et al. 2002).

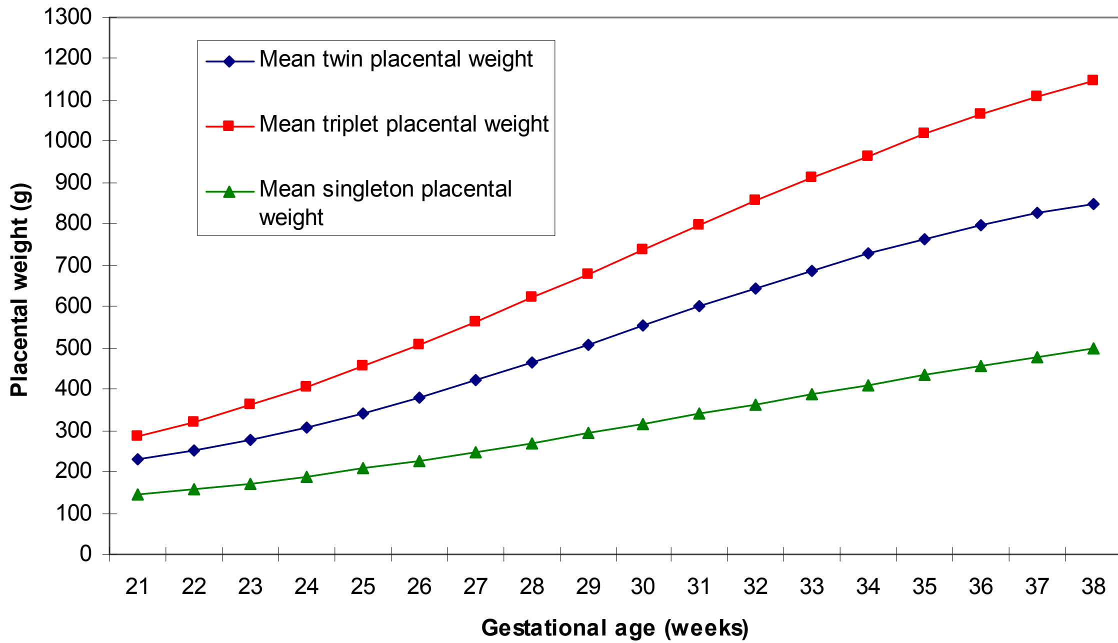


Figure 25: Comparison of trimmed singleton, twin and triplet placental weights between 21st and the 38th week modified from Pinar et al. (1996) and Pinar et al. (2002).

Figure 25 compare the different mean placental weights of singleton, twins and triplets between the 21st and the 38th week. The data are based on the examination of 714 singleton, 514 twin and 196 triplet trimmed placentas. The mean singleton placental weight curve rises almost linearly while for twin and triplet placentas an acceleration of the placental weight gain from the 24th week can be observed.

Table 6: Comparison of singleton, twin and triplet placental weights, at 38weeks, and the calculated placental weight per fetus. Data according to Pinar et al. (1996) and Pinar et al. (2002).

Pregnancy	**Placental weight (g)** (38th pregnancy week)	**Placental weight per fetus (g)**	**Reference**
Singleton	499	499	Pinar et al. (1996)
Twin	850	425	Pinar et al. (1996)
Triplet	1147	382	Pinar et al. (2002)

The mean values of triplet placental weight per fetus at the 38th are 23% lower than those of singleton placentas (Pinar et al. 2002).

Bleker et al. (2006) reported that the mean twin placental weight in comparison to the mean singleton placental weight is smaller from the 22 week on while the mean birth weight of twin children is lower from the 32nd week , with a maximum difference about 600g at the 39th -40th week.

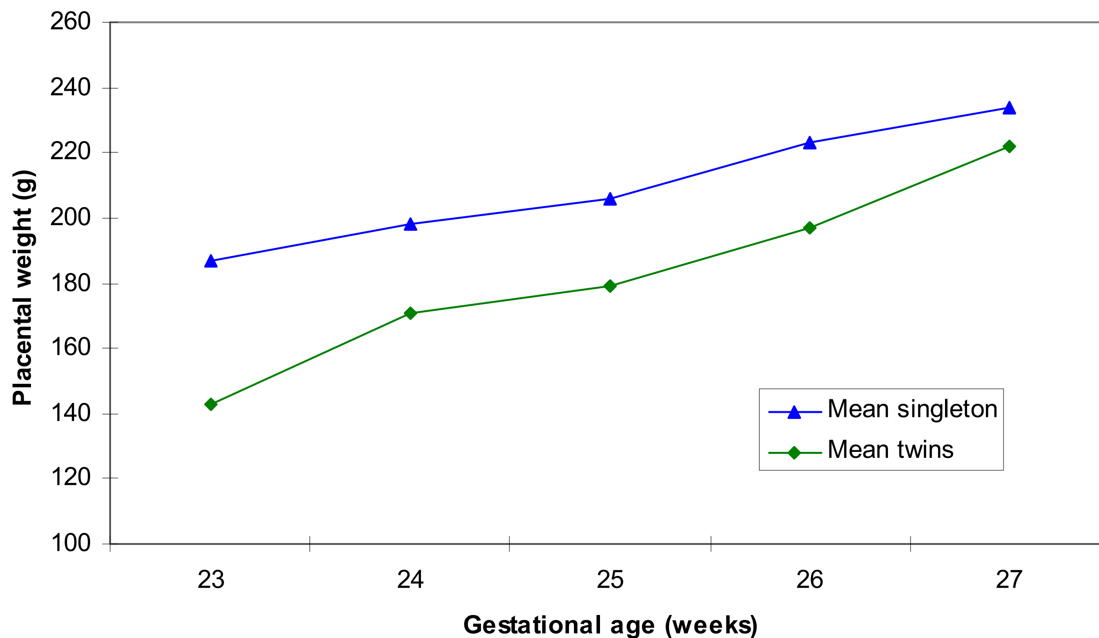


Figure 26: Trimmed singleton and twin placental weight comparison between the 23rd and the 27th pregnancy week modified from Hecht et al. (2007).

Figure 26 describes the weight difference of singleton placental weight and unfused twin placentas from the 23rd week until the 27th week. The data are based on 840 singleton and 197 unfused twin placentas, which were weighed after trimming cord and membrane. The placental weights of unfused twin placentas are smaller at these gestational ages.

In another study (Gielen et al. 2006) data of 4318 twin pair placentas were analyzed. Placentas were weighed after removing the membranes and blood clots and were divided in two different groups:

1) one placenta mass
2) two separate placentas

Placental weight increases up to the 42nd week with a maximum increase at the 28 weeks. Furthermore the total placental weight was higher in cases with two separate placentas. However the weights were similar up to 30 weeks and only thereafter the total weight of two separate placentas increased with a maximum difference of 39g at 42 weeks (Gielen et al. 2006).

Conclusion: Also twin and triplet placental weight increases continuously throughout gestation. However the placental weight per fetus at a twin pregnancy, at the 38th pregnancy week, is at mean 74g and in case of a triplet pregnancy 117g lower than singleton placental weight.

3.6.1. PLACENTAL WEIGHT INCREASE PER WEEK

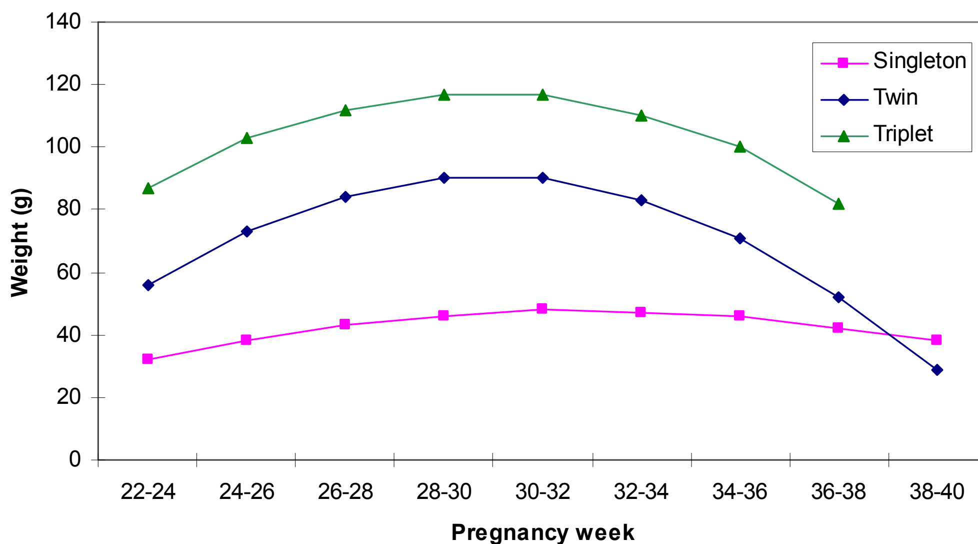


Figure 27: Comparison of the biweekly placental weight increase in singleton, twin and triplet pregnancies calculated from the data of Pinar et al. (1996) and Pinar et al. (2002).

Conclusion: Singleton placental weight shows a constant increase until term, whereas the twin and triplet placental weight increase per week show a continuous decrease beginning at the 32nd-34th pregnancy week.

3.7. INFLUENCE OF ETHNICITY ON PLACENTAL WEIGHT

Placental weight may be determined by genetic background, hence it may vary between different ethnicities.

Birth weight differences between several ethnicity groups are described in few studies (Sivarao et al. 2002; Perry et al. 1995; Salafia et al. 2008). The mean birth weight of white babies, delivered at the 40th week, is 156g higher than that of non-white babies (Hendricks 1964).

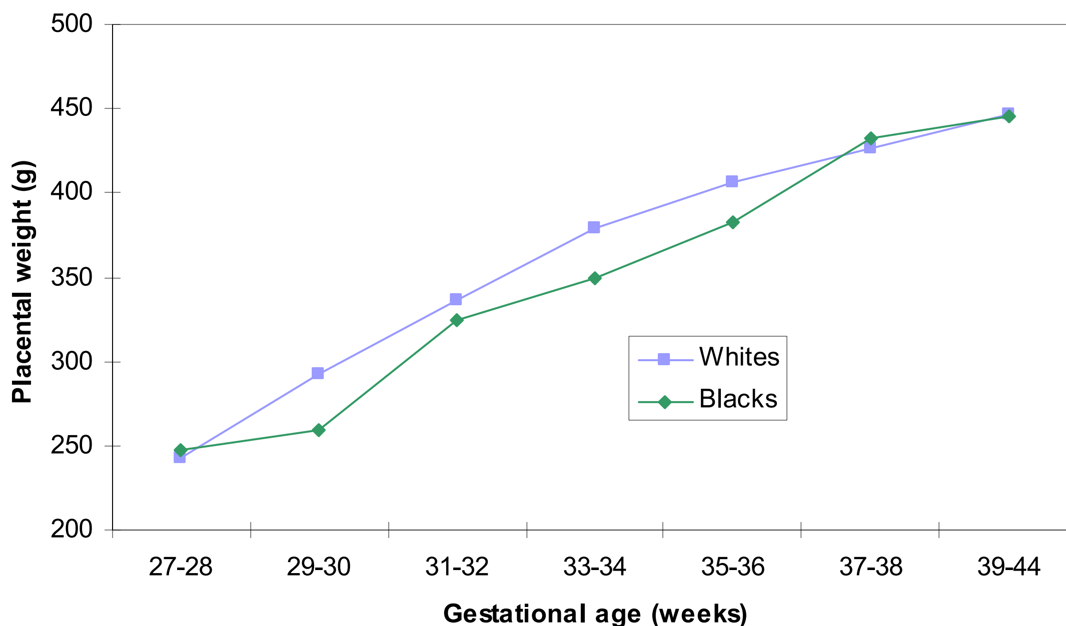


Figure 28: Placental weight associated with white and black ethnicity between the 27th-44th gestational week modified from Naeye (1987).

During the years 1959-1966 in different hospitals in the United States trimmed placental weight of 20 724 white and 17 627 black children was measured. Placental weights of blacks were lower throughout gestation however at term no significant placental weight difference could be found (Figure 28; Naeye 1987).

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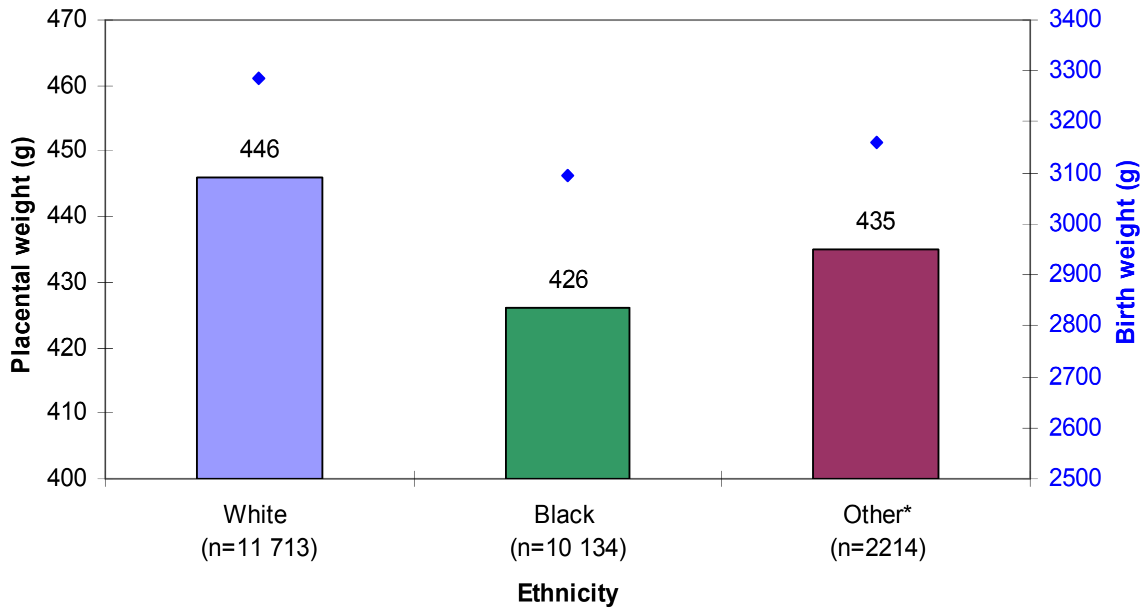


*Other: most of them are Puerto Ricans

Figure 29: Comparison of trimmed placental weight related to ethnicity between the 34th -42nd gestational week modified from (Salafia et al. 2008).

In the largest study (Figure 29) trimmed placental weights of 24,061 subjects delivered from 34th-42nd gestational week were included in the observations. Significant higher placental weights and birth weights were observed in the “White” study population (Salafia et al. 2008).

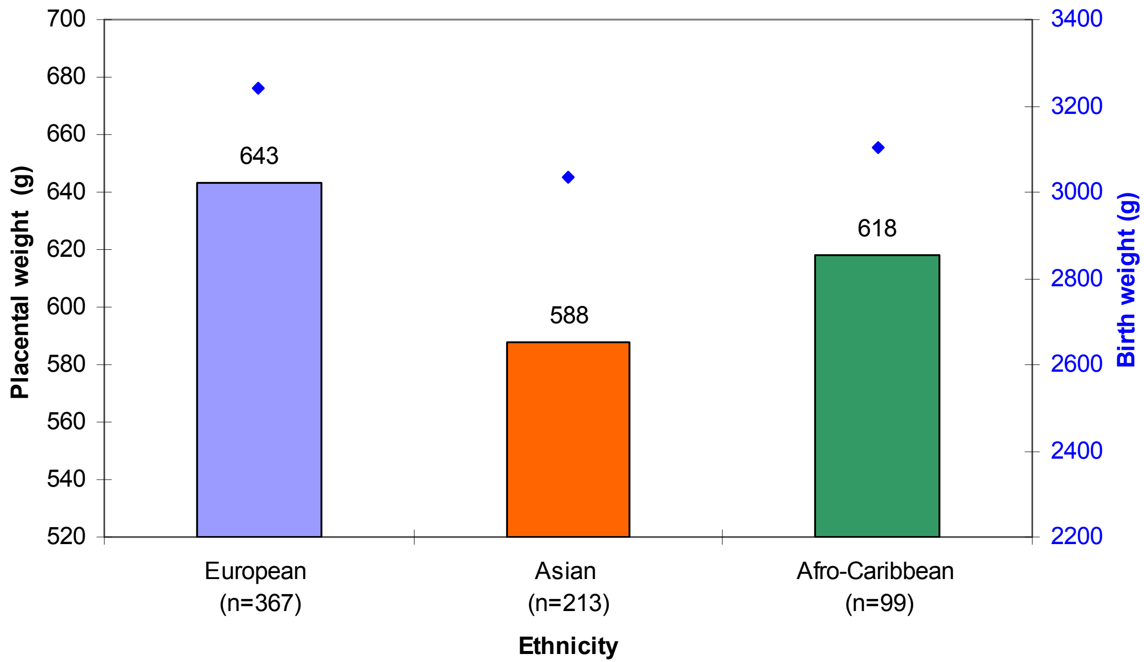


Figure 30: Untrimmed placental weight associated with ethnicity delivered between 39th - 41st pregnancy weeks modified from (Perry et al. 1995).

Untrimmed placental weights of three different ethnicities delivered between the 39th-41st pregnancy weeks were compared. Placental and birth weight were higher in the European and Afro-Caribbean group compared with Asians. However, no significant difference of the placental weight ratio was observed suggesting no difference in placental efficiency to sustain fetal growth in these ethnicities (Figure 30; Perry et al. 1995).

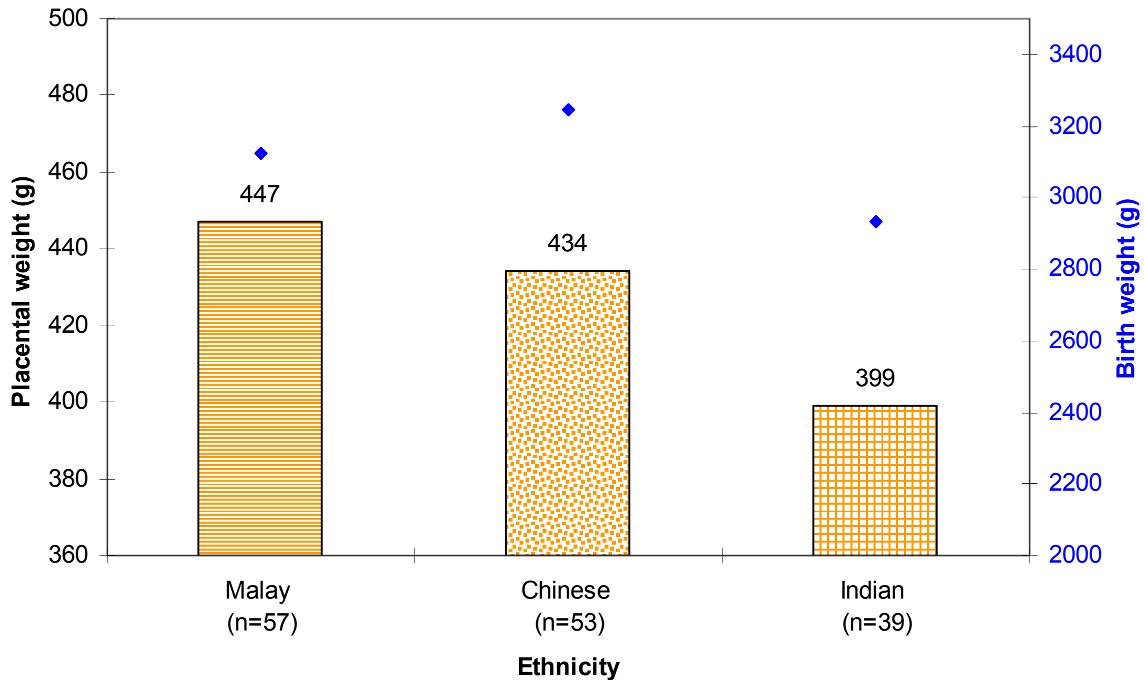


Figure 31: Relationship of trimmed placental weight and ethnicity between the 37th-42nd pregnancy weeks modified from (Sivarao et al. 2002)

Within Asians placental weights of trimmed placentas delivered between the 37th-42nd pregnancy weeks were compared (Figure 31). The placental weight of the Indian study population is lower than that of Malayan and Chinese. Moreover a lower placental volume, placental surface area, infants birth weight and length compared to the other two groups are described (Sivarao et al. 2002).

Table 7: Comparison of the fetal-placental weight ratio in association with ethnicity, data according to Perry et al. (1995), Sivarao et al. (2002), Salafia et al. (2008).

Ethnicity	Fetal-placental weight ratio	Reference
European	5	Perry et al. (1995) (untrimmed placental weight)
Asian	5.1	
Afro-Caribbean	5	
Malay	7	Sivarao et al. (2002) (trimmed placental weight)
Chinese	7.4	
Indian	7.3	
White	7.3	Salafia et al. (2008) (trimmed placental weight)
Black	7.2	
Other	7.2	

Conclusion: The previous illustrations show that ethnicity is also a main factor influencing the placental weight. However it must be considered that no significant differences of the fetal-placental weight ratio associated with the ethnicity were determined except in the Malayan population (Sivarao et al. 2002)

3.8. INFLUENCE OF MATERNAL NUTRITION ON PLACENTAL WEIGHT

The following part focuses on the impact of the maternal nutrition on placental growth, especially on the intake of energy, carbohydrate, fat, protein and vitamins.
Godfrey et al. (1996) reported placental and birth weights of 538 term pregnancies with trimmed placentas related to maternal nutrition in early and late pregnancies.

Early pregnancy:

Table 8: Placental and birth weight depending on maternal energy, carbohydrate, fat and protein intake in early pregnancy; data according to Godfrey et al. (1996).

Intake	Placental weight (g)	Birth weight (g)	Fetal-placental weight ratio	No of subjects
Energy (g):				
</=2080	547	3468	6.3	180
-2560	535	3446	6.4	173
>2560	520	3412	6.6	185
Carbohydrate (g):				
</=265	554	3501	6.3	181
-340	531	3444	6.5	172
>340	517	3381	6.5	185
Fat (g):				
</=80	542	3456	6.4	191
-105	543	3461	6.4	165
>105	517	3409	6.6	182
Protein (g):				
</=76	537	3462	6.4	175
-95	536	3427	6.4	175
>95	528	3437	6.5	188

Intake in early pregnancy:

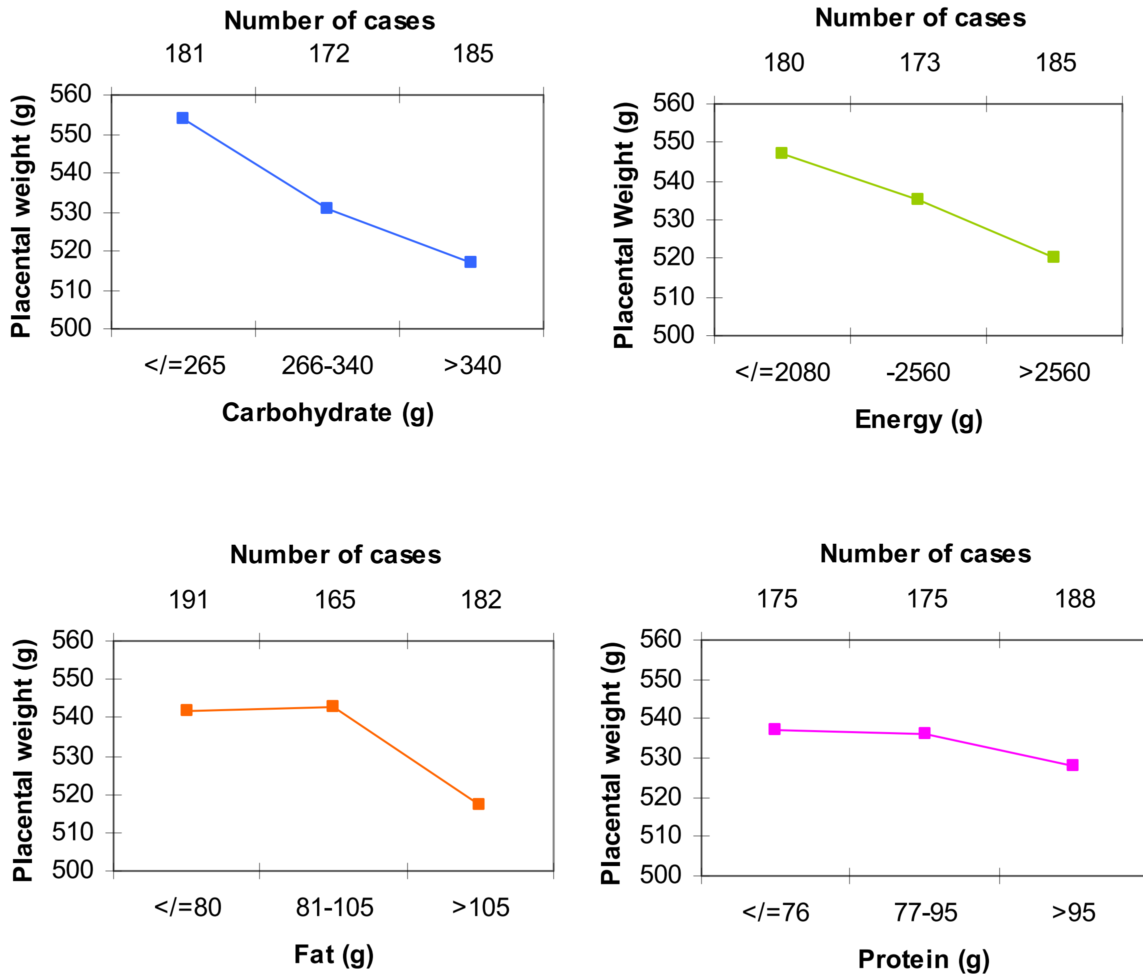
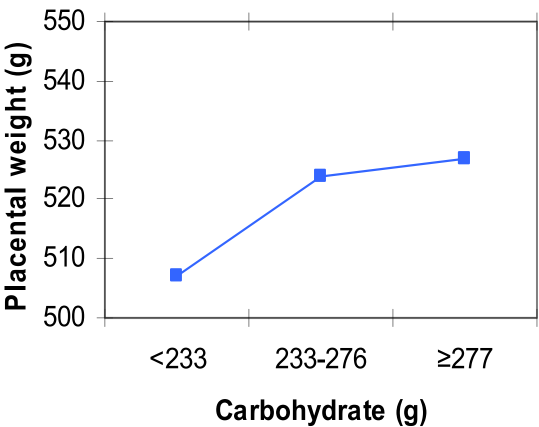


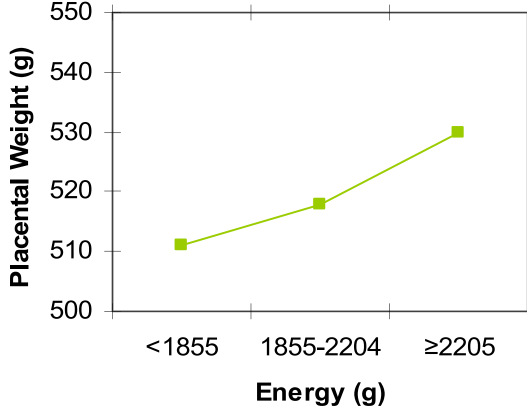
Figure 32: Placental weight depending on maternal energy, carbohydrate, fat and protein intake in <u>early</u> pregnancy modified from Godfrey et al. (1996).

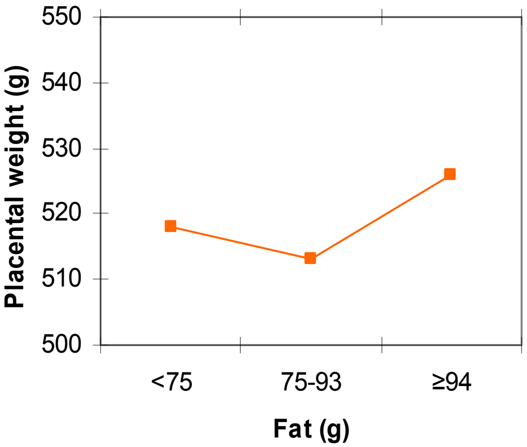
Placental and birth weight decreased when the mother ingests high carbohydrates in <u>early</u> pregnancy, placental weight was reduced by 49g for each log g increase of carbohydrate intake. Generally, it has been observed that the relation between energy intake in early gestations and placental as well as birth weights are inverse (Godfrey et al. 1996).

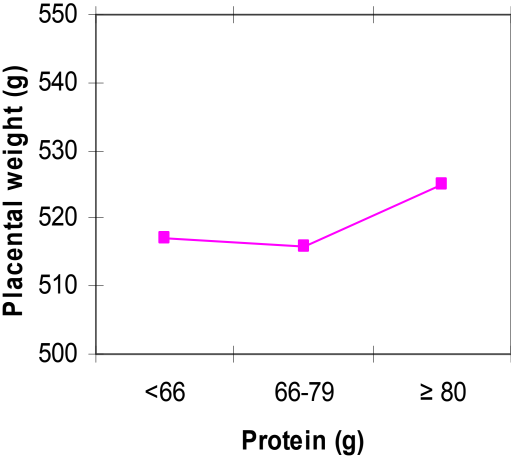
Another study which observed the relation between maternal nutrition during early gestation and the placental weight took place in Portsmouth, UK, between May 1994 and February 1996 with 640 placenta samples (Mathews et al. 1999).

Intake in early pregnancy:









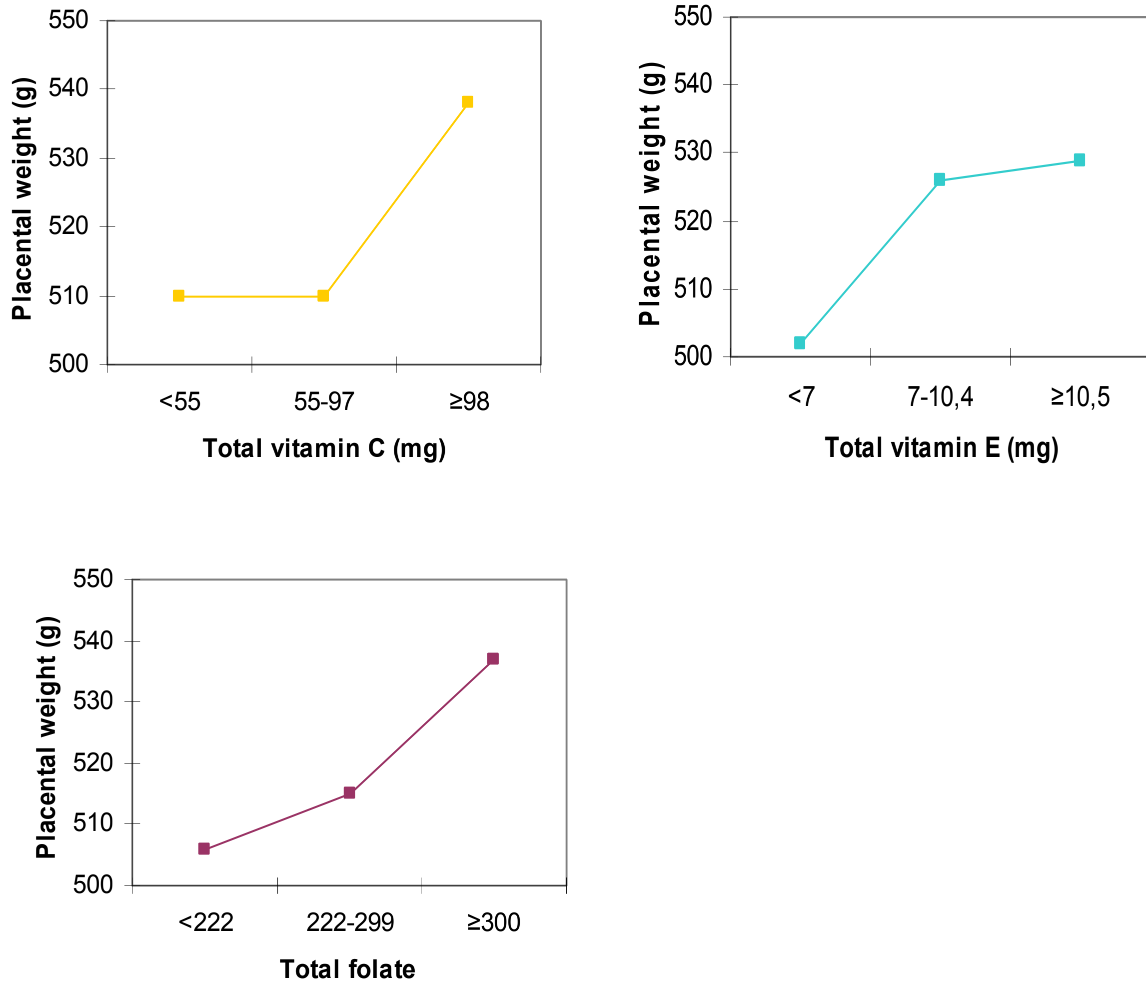


Figure 33: Placental weight related to maternal energy, carbohydrate, fat, protein, vitamin C, vitamin E and folate intake in early gestation modified from Mathews et al. (1999).

Increase of the total vitamin C and total folate affected the placental development positively while carbohydrate, energy, fat, protein and vitamin E intake did not show that high effects.

Late pregnancy:

Table 9: Placental and birth weight depending on maternal energy, carbohydrate, fat and protein intake in late pregnancy; data according to Godfrey et al. (1996).

Intake	Placental weight(g)	Birth weight (g)	Fetal-placental weight ratio	No of subjects
Energy (g):				
</=2080	537	3452	6.4	175
-2560	531	3438	6.5	182
>2560	534	3436	6.4	185
Carbohydrate (g):				
</=265	544	3492	6.4	170
-340	529	3427	6.5	190
>340	530	3409	6.4	178
Fat (g):				
</=80	538	3443	6.4	165
-105	530	3432	6.5	187
>105	534	3450	6.5	186
Protein (g):				
</=76	530	3419	6.5	173
-95	534	3453	6.5	189
>95	537	3452	6.4	176

Intake in late pregnancy:

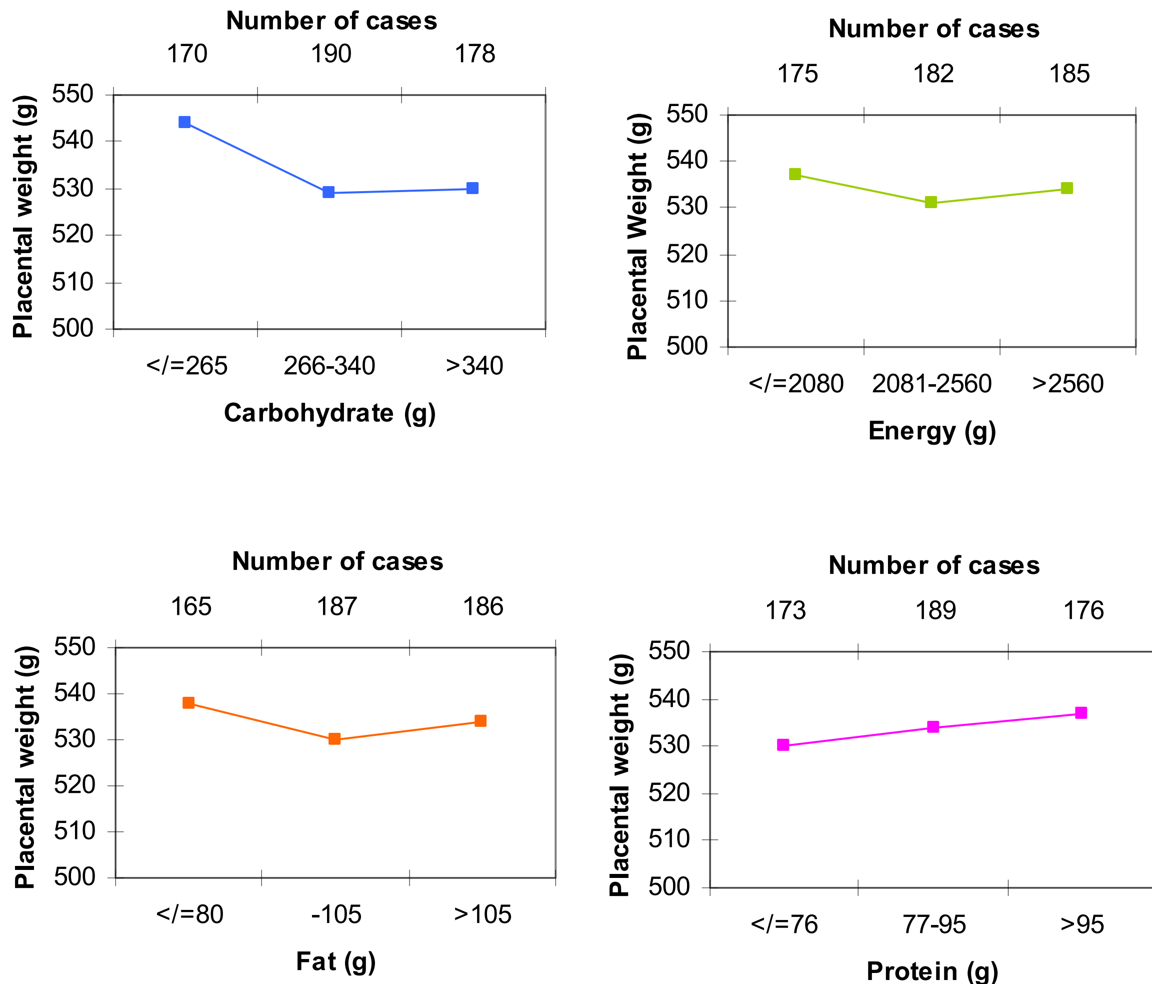


Figure 34: Placental weight depending on maternal energy, carbohydrate, fat and protein intake in late pregnancy modified from Godfrey et al. (1996).

Godfrey et al. (1996) described in his studies that low placental weight goes along with low intake of dairy protein relative to carbohydrate in late gestation. Higher placental and birth weights are correlated with high intakes of iron and folate from supplements in late gestation.

Moreover a reduction of nutrient intake in early gestation decreases maternal levels of insulin and the insulin like growth factor 1 (IGF-1). This secures a proper nutrient availability, placental transport and development of placental growth (Huxley R. 2000; Godfrey et al. 1995).

Table 10 shows the maternal weight, the birth weight and the placental diameter as a proxy measure of weight (cf. pp. 26, 27); at birth associated with the maternal nutrition during the third trimester. A positive correlation between the birth weight and the caloric and the protein/carbohydrate intake in the third trimester can be observed. However no impact on the placenta diameter can be observed.

Table 10: Placental diameter and birth weight depending on the caloric intake in the 3rd trimester modified from Roseboom (2000).

Caloric intake in 3rd trimester	Maternal weight (kg)	Birth weight (g)	Placental diameter (cm)	Number of subjects
<1000	62.8	3146	19.6	168
1000-1250	65.5	3252	20.2	39
1250-1500	66.5	3426	21.0	89
1500-1750	65.4	3346	20.3	127
1750-2000	67.4	3476	20.0	71
>2000	65.6	3439	20.2	245

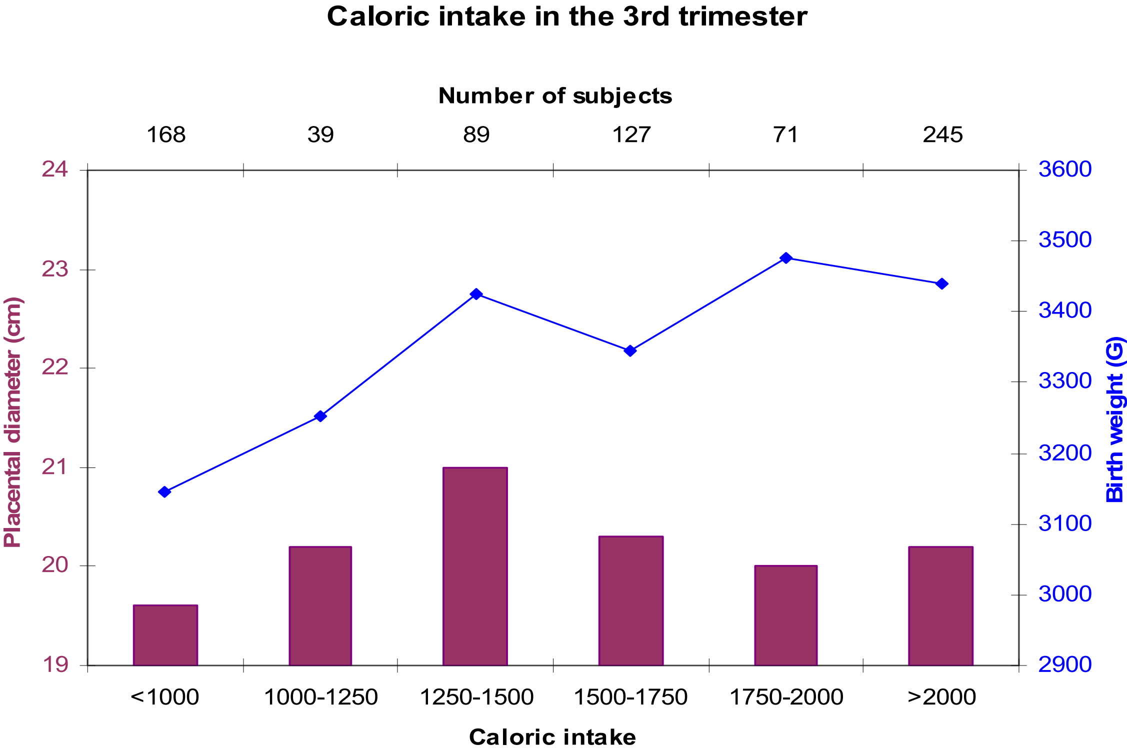


Figure 35: Placental diameter and birth weight related to caloric intake in the 3rd trimester modified from Roseboom (2000).

Table 11: Placental diameter and birth weight related to Protein/carbohydrate intake in the 3rd trimester: data according from Roseboom (2000).

Protein/ carbohydrate in 3rd trimester (%)	Maternal weight (kg)	Birth weight (g)	Placental diameter (cm)	Number of subjects
<15	62.9	3157	19.0	107
15-16	65.9	3344	20.8	167
16-17	66.0	3364	20.4	176
17-18	68.3	3427	20.2	75
18-19	69.8	3350	20.1	52
19-20	64.3	3354	19.6	61
>20	68.0	3470	20.2	101

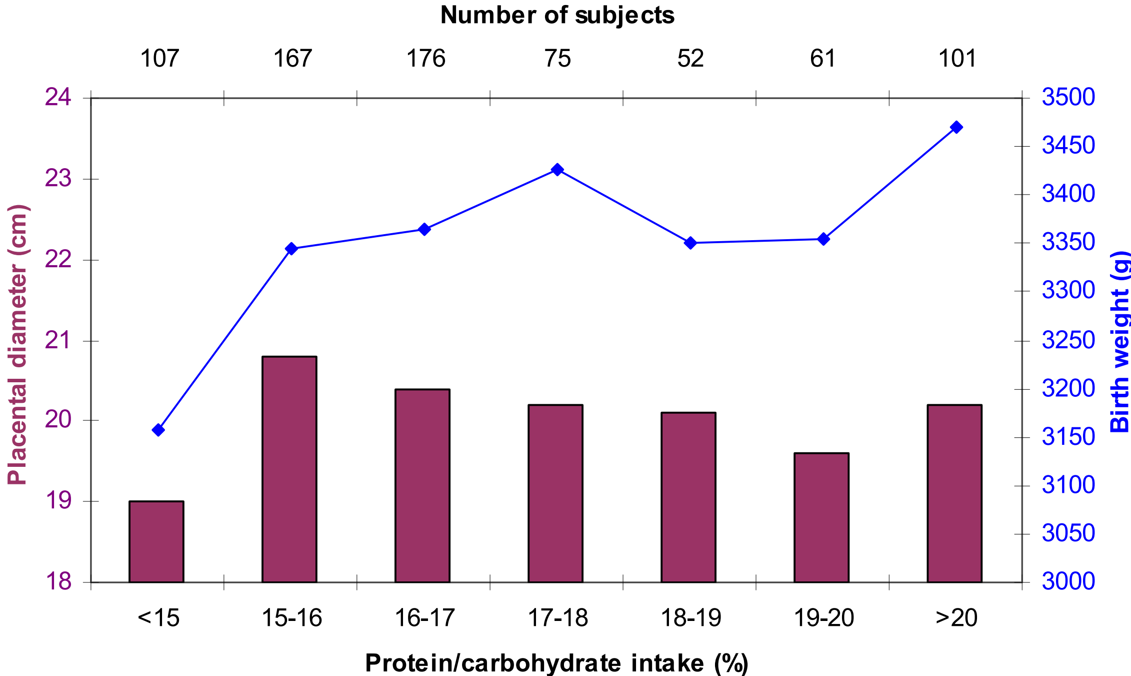


Figure 36: Placental diameter and birth weight related to protein/carbohydrate intake in the 3rd trimester modified from Roseboom (2000).

Conclusion: A positive association of placental weight increase and the decrease of carbohydrate and energy intake, as well as increased total folate and vitamin C intake in

early pregnancy is reported. In late pregnancy on the other hand only low carbohydrate intake could be associated with an increase in placental weight.
The highest placental diameter was described for a caloric intake of 1250-1500 in the 3rd trimester and a protein/carbohydrate intake ratio between 15-16%.

3.8.1. INFLUENCE OF MATERNAL UNDERNUTRITION ON THE PLACENTA

Reduced energy intake in early pregnancy has a positive effect on placental growth and subsequently on fetal growth. Infants are born with birth weights within the normal range and with an increased placental weight when a period of undernutrition took place only during the first trimester, which indicates that undernutrition in the first trimester of pregnancy resulted in compensatory placental growth. On the contrary an increased food intake at an early time of gestation is associated with lower placental and birth weights (Huxley 2000). Moreover Bortolus et al. (1998) described that undernutrition during pregnancy depending on timing and extent of undernutrition can inhibit or stimulate placental growth. Mild undernurition ensued an increase in placental growth, whereas severe maternal undernurition leads to a restriction of placental and fetal growth (Bortolus et al. 1998). Godfrey et al. (1995) reported that experimental studies in sheep have shown that a period of undernutrition in mid pregnancy has several implications regarding the maternal weight at booking. If sheep with a low weight at booking were exposed to a further period of undernutrition, the fetal and placental growth was negatively influenced. On the other hand mothers who were well nourished at booking show placental hypertrophy. Moreover it is reported that fetuses start to grow faster when the mothers suffer from undernutrition in the last trimester. "In such fetuses, on a fast growth trajectory, maternal undernutrition may result in fetal wasting and consumption of fetal amino acids by the placenta in order for it to maintain lactate output to the fetus" (Godfrey et al. 1995).

However, data exists about humans who had to cope with undernutrition in pregnancy. During the Second World War from 1944 to 1945 the Netherlands had to experience a great famine called the "Dutch famine". The allied force liberated the South of the country but thereafter the operation `Marked Garden´ failed and food supply was sparse in the Northern and especially in the Western parts of the Netherlands. The daily caloric rations in December 1943 were 1800 calories for the general adult population. In November 1944 the caloric intake was just 1000 caloric and between December 1944 and April 1945 the daily calorie rations decreased to 400-800 calories. After the liberation in May 1945 the situation normalized (Roseboom 2000).

Over this period of famine, birth weights and placental weights were well documented. An association of fetal and placental growth in connection with the timing of undernutrition during pregnancy could be observed.

Table 12: Birth weight and placental weight development during the Dutch famine: data of Lumey (1998).

Month of birth	Exposure in relation to pregnancy trimester	Birth weight (g)		Placental weight (g)		Placental index		Number of subjects	
		West	North	West	North	West	North	West	North
Aug 1944-Oct. 1945	„Pre-famine“ Controls: exposed after birth	3372	3386	605	667	18.0	20.0	109	160
Nov 1944-Jan. 1945	Intermediate exposure category	3232	3330	557	622	17.4	19.1	94	172
Feb 1945-Apr. 1945	Third	3050	3209	511	583	17.1	18.4	107	225
May 1945-Jun. 1945	Third and second	3104	3174	540	557	17.9	17.6	69	121
Jul. 1945	Second	3399	3470	570	652	16.8	19.0	43	52
Aug. 1945-Sep. 1945	First and second	3388	3305	601	667	18.1	20.5	51	129
Oct. 1945-Dec. 1945	First	3368	3353	599	694	18.1	20.9	105	182
Jan. 1946-Mar. 1946	„Post-famine“: exposed before conception	3345	3346	600	678	18.2	20.8	187	245

Placental index= placental weight/birth weight x 100%

These data (Table 12) were collected in two different hospitals, one in the Western part of the Netherlands affected of a severe famine and the other in the North where the food ratios were low but not as bad as in the Western part.

It can be noticed that the placental weight and the placental index was increased in infants, who were exposed to undernutrition in the first trimester, while there was no effect on birth weight.
When the pregnancy was exposed to undernutrition in the third trimester of gestation the placental weight, the PI and the birth weight were decreased (Lumey 1998).

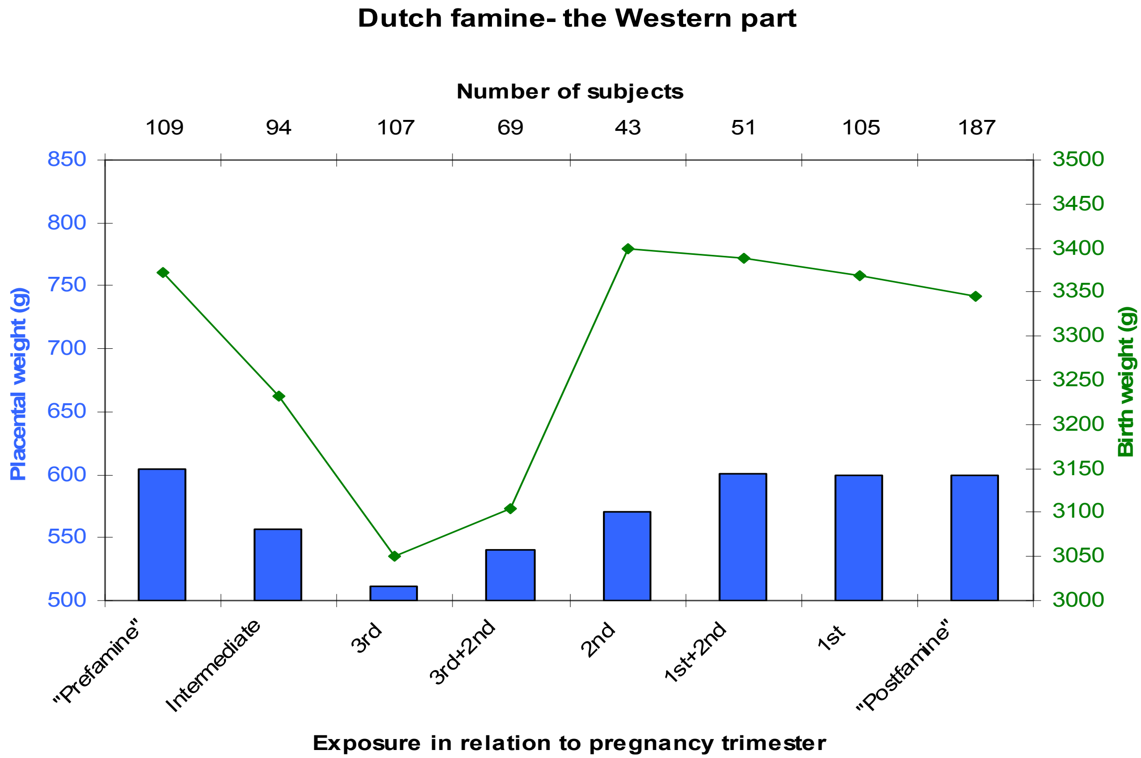


Figure 37: Placental and birth weight development during the Dutch famine in the Western part modified from Lumey (1998).

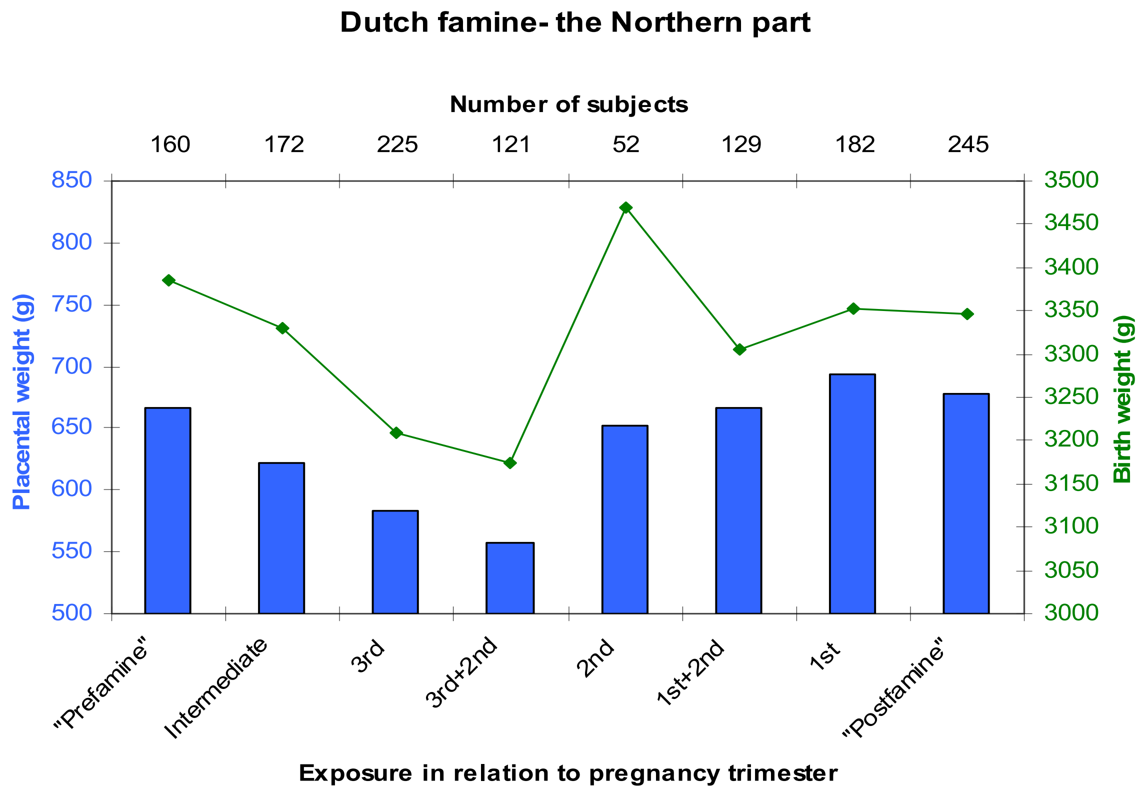


Figure 38: Placental and birth weight development during the Dutch famine in the Northern part modified from Lumey (1998).

A further report (Rosso 1980) describes changes in placental growth from undernourished women and women living in developing countries under poor conditions. Generally, placentas of these women have an almost 14-50% lower mean placental weights than well nourished women. Moreover reduction in DNA content, which shows a proportional bigger decrease and protein/DNA ratios are reported. On the basis of these changes it was assumed that the phase of hyperplastic growth is proportionally more affected than hypertrophic growth of the placenta. Furthermore placentas from poor Guatemalan women were compared with middleclass American women. Placentas from Guatemalan women show a reduction of the peripheral villous mass, trophoblastic mass, the peripheral villous surface, and peripheral villous capillary surface. Particularly the reduction of villous surface indicates a decrease of maternal-fetal exchange area with consequences on the maternal-fetal transfer (Rosso 1980).

Conclusion: Maternal undernutrition in the 1st and 2nd trimester leads to equal or higher placental and birth weight, while undernutrition affecting the 2nd and 3rd trimester is associated with significantly lower placental and birth weights.

3.8.2. INFLUENCE OF THE MATERNAL OBESITY ON PLACENTAL WEIGHT

The number of obese pregnant women has been rising over the past decades. Here it will be analyzed if and how THIS has affected placental weight. The maternal body mass index (kg/m²) is used as an index of obesity.

Naeye (1987) reported that underweight mothers were associated with placental undergrowth.

Thomson et al. (1968) described that tall and heavy mothers were associated with larger placentas than short and lighter mothers. Moreover; factors which are associated with low placental weight were low maternal height and mothers with deceasing maternal BMI (Godfrey et al. 1996). Additionally, it was reported that the maternal body mass index is positively associated with placental weight to birth weight ratio (Heinonen et al. 2001). Large placental weight and a high placental ratio are the result of maternal nutritional deficiency, which causes placental hypertrophy that is disproportionate to fetal size (Godfrey et al. 1995). Furthermore an increase in the maternal BMI which correlates strongly with the increase in the placental weight was observed in this study. Additionally an inverse relation between the pre-pregnancy BMI and the total weight gain from the mother during gestation was reported (Swanson et al. 2008). Furthermore it is reported that the higher body mass, of women (BMI of 27 or more), has shown a significant correlation with higher placental index than pregnant women with a lower BMI (Little et al. 2003). Williams et al. (1997) described that small maternal pelvic diameter which is a potential marker for poor nutrition during development is related to significantly increased placental weight to birth weight ratios. Furthermore poor nutrition before and during gestation is a factor determining the birth weight relative to placental weight, while high maternal BMI at booking is positively related with the placental weight to birth weight ratio. Also Sivarao et al. (2002) explained that both placental weight and volume are correlated with the maternal booking weight.

Conclusion: High maternal body mass index is associated with high placental weight.

3.8.3. INFLUENCE OF NAUSEA AND VOMITING ON PLACENTAL GROWTH

Another factor influencing placental growth which is discussed is nausea and vomiting during pregnancy (NVP). Morning sickness which is characterized by nausea and vomiting is experienced by up to 70% of pregnant women. It begins during the first few weeks of pregnancy and persists for about 3 month. This time period is associated with rapid placental growth and production of human chorionic gonadotrophin and an increased secretion of thyroxine, a potent placental growth stimulator. Nausea and vomiting were more frequent among young women weighing 77 kg or more than women with normal or lower BMI (< 19). It was even observed that women with a low BMI enlarge their energy intake during each trimester and gain more weight during gestation. Women with a high value of BMI however decrease their energy intake and lose substantial amounts of peripheral fat throughout pregnancy. Women with nausea and vomiting are typically show favourable pregnancy outcomes such as decreased risk of miscarriage perinatal death, low infant birth weight, and preterm birth. On the other hand women who experienced no symptoms of nausea and vomiting show a higher incidence of spontaneous abortion and deliver a larger proportion of low birth weight (LBW) infants (Huxley 2000). Furthermore Czeizel et al. (2004) describes that nausea and vomiting in pregnancy is related to lower proportion of preterm births and a slightly longer gestational age of newborn infants. The consecutions of those changes are that the mean birth weight is somewhat higher and a lower proportion of low-birth weight newborns were observed. Two different hypotheses are discussed on the one hand: nausea and vomiting in pregnancy severe as a protector against food, which poses potential danger to the embryo. So foods and foodborn pathogenic micro-organisms that comprise teratogenic and abortifacient toxic chemicals are vomited or the pregnant mothers abstain such food. On the other hand women with nausea and vomiting in pregnancy have larger placentas, a higher blood level of human chorionic gonadotrophin and oestrogens which have an excitatory effect on the gestational age. Furthermore it is reported that girls are more frequently delivered by mothers with severe nausea and vomiting in pregnancy (Czeizel et al. 2004).

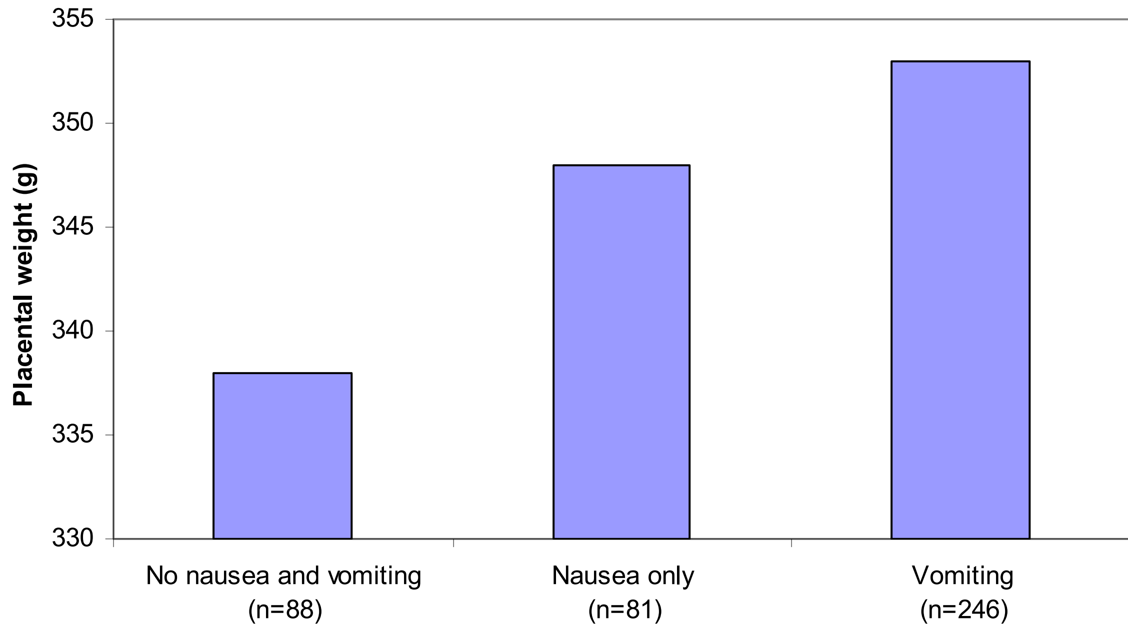


Figure 39: Trimmed placental weight (delivered after the 28th gestational week) in association with nausea and vomiting of pregnancy modified from Weigel et al. (2006).

Figure 38 describes a positively association between nausea and vomiting of pregnancy and placental weight increase. As well as discussed previously nausea and vomiting in pregnancy was also associated with a decreased risk of preterm delivery or congenital anomaly (Weigel et al. 2006).

Conclusion: Women who are affected of nausea and vomiting generally show favourable pregnancy outcomes such as decreased risk of miscarriage; perinatal death and low infant birth weight, lower proportion of preterm birth and a slightly longer gestational age of newborn infants. Furthermore an increased placental weight in association with nausea and vomiting of pregnancy can be observed.

3.9. INFLUENCE OF MATERNAL EXERCISE ON PLACENTAL WEIGHT

The influence of maternal exercise during pregnancy on the placental development has often been discussed. However it is important to take into account both the intensity and the period of pregnancy in which the exercise will be performed.

For example starting an appropriate-intensity of weight bearing exercise during early gestation and going on throughout pregnancy stimulates the rate of mid-trimester growth in placental volume at term. Moreover high volume weight bearing exercise work out during the first half of gestation with a decrease of intensity by 50%-70% leads to an increase in growth of the intervillous space, the villous tree and an increase in birth size. Continuing an appropriate intensity of weight bearing exercise throughout gestation does not result in an obvious change in the infants size at term. In contrast women who increase the exercise intensity to or over the one in pre-gestation in late pregnancy are likely to show decreased mid-trimester placental volume and typically give birth to the lightest, leanest babies with the greatest feto-placental weight ratio (Clapp 2006; Bergmann et al. 2004).

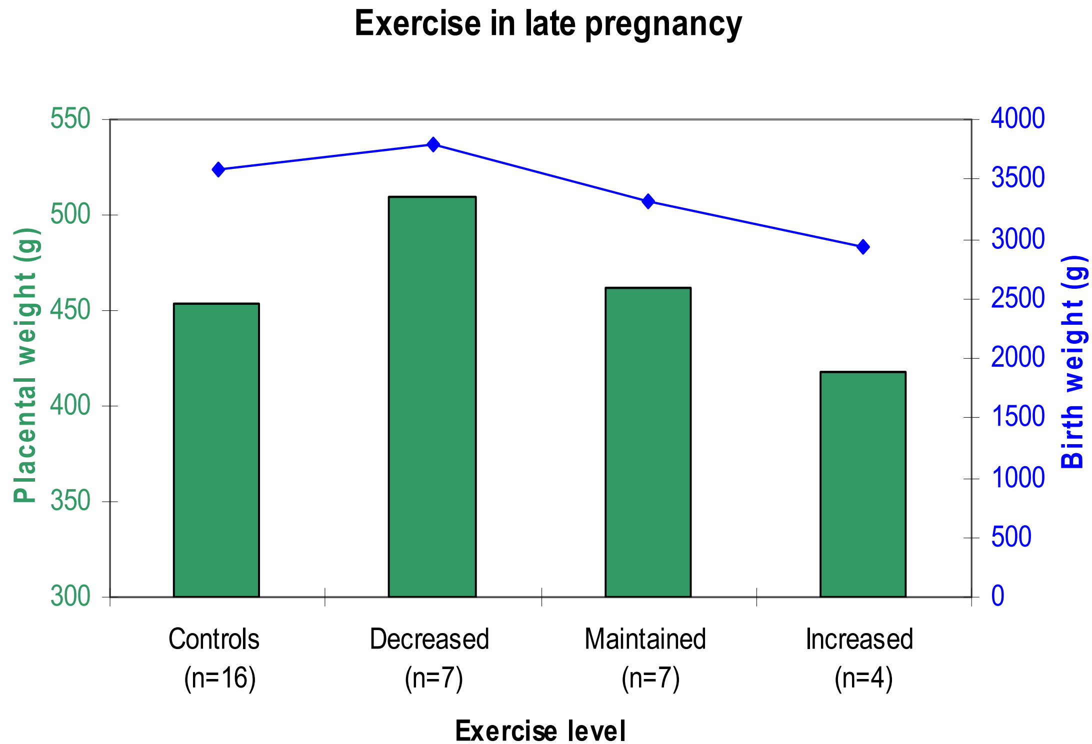


Figure 40: Modified version of a placental and birth weight development scale depending on the level of exercise in late pregnancy from Clapp et al. (1992), which did not define exactly gestational week analyzed.

Women in the exercise group performed aerobics (n=9), swam (n=5) or ran (n=4) at least three times a week for about 20 minutes. The intensity of these sessions was about ≥ 50% of the maximum preconceptional intensity. The result was an inverse relationship between the placental- and birth weight and the intensity of the exercise performance in late pregnancy (Figure 40; Clapp et al. 1992).

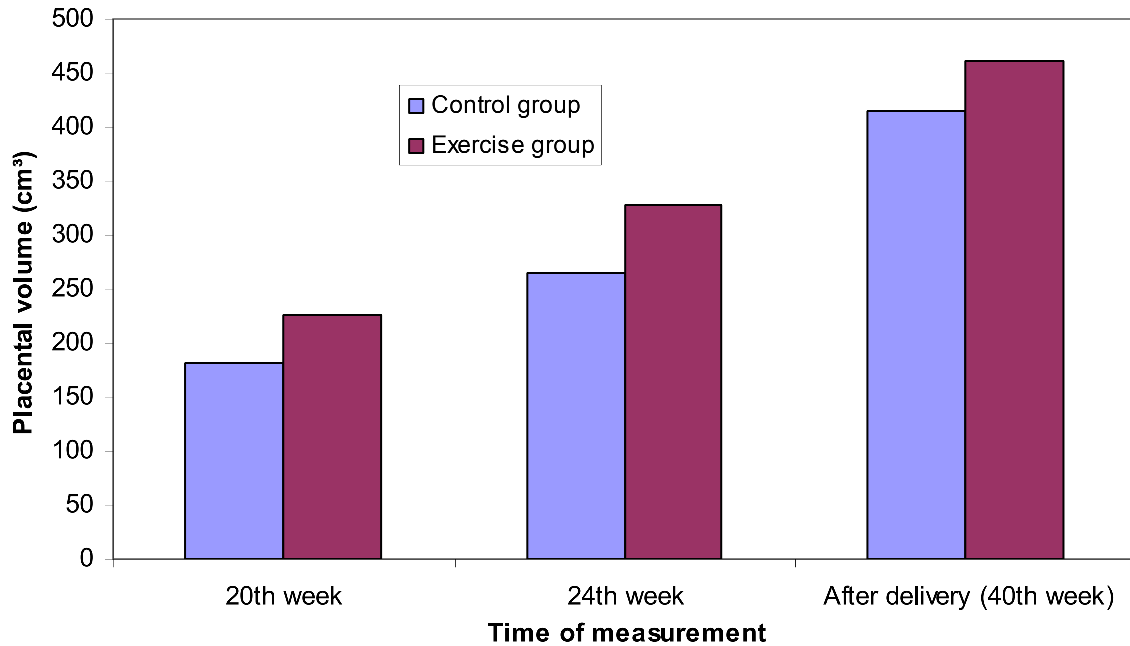


Figure 41: Changes of a placental volume over the second half of gestation depending on exercise from Clapp et al. (2000).

The placental volume at the 20th and the 24th pregnancy week as well as after delivery (40th gestational week) was significantly greater in the exercise group compared to the controls (Figure 41).

Women in the exercise group performed 20 minutes of weight-bearing exercise, like workout on a treadmill, step aerobics, or stair stepper, three to five times a week throughout pregnancy with an intensity between 55% and 60 % of their maximum exercise intensity before pregnancy. The control group did not practice any weight-bearing exercise. Placenta volume was measured using a B-mode ultrasonography and fixed arm transducer during gestation. Values after delivery were determined from trimmed placentas (Clapp et al. 2000).

Conclusion: Performing weight bearing exercise at an intensity of 50% of the maximum preconceptional intensity throughout pregnancy leads to an increase in placental volume. However, the highest average placental- and birth weight at term could be observed when the exercise level was decreased in late pregnancy.

4. SUMMARY AND DISCUSSION

In the past decades many observations of the fetal development as well as of the fetal weight gain throughout pregnancy have demonstrated their great importance for detecting pathologic changes in utero. To assist the obstetrician's monitoring of the fetal weight gain, birth weight-percentile-curves were established. Although in the past the weight of the placenta has received less attention than the birth weight, it is a very and important significant parameter for the assessment of the ongoing pregnancy and when measured at delivery for detecting problems during pregnancy. Especially it would be a good parameter to detect pathologic changes at an early stage, because of the rapid placental growth compared to the fetal development in early pregnancy. With this knowledge it would be possible to intervene earlier and try to positively influence the fetal development.

The present review has focussed on placental weights of uncomplicated pregnancies and has only considered results obtained at low level altitude.

Establishing useful placental weight percentile curves is a complex task. It is very difficult to compare placental weights weighed by different investigators, because the <u>mode of preparation</u> before weighing plays a major role. Some of the investigators weigh the placentas without any preparations, whereas other scientists remove the membranes and the cords. However, the extent of blood draining influences the weight as well. Scientists tried to determine the weight differences between untrimmed (with higher weight) and trimmed placentas in order to make the comparison possible, and found a difference on average of 16% between both preparations. In this context also the mode of the delivery has to be considered. The weight difference between untrimmed and trimmed placentas in case of vaginal delivery is 19%, while it is only 14% for delivery by Caesarean section. An explanation for this effect of delivery is that the cord is cut closer to the fetus in vaginal deliveries, which leads to a higher untrimmed placental weight (Lary et al. 2003; Dombrowski et al. 1994).

When <u>placental weight in singleton pregnancies</u> is compared between the 27th and the 40th week of pregnancy a continuous increase until term can be observed. At week 40 the placental weights range between 470g and 537g. These weights were determined using trimmed placentas.

Several factors influencing placental growth were investigated in this review. Within the last century a continuous increase of placental weight was observed, which, as a hypothesis, may result from increasing birth weight and length of the infants (Tretyak et al. 2005). The high variance of the placental weights reported in the literature may be partly result from the various ethnic groups included in the studies. For example a slight placental weight difference among Whites and Blacks in favor of the White population is described (Salafia et al. 2008). Besides the differences between Whites and Blacks the placental weight of Europeans is higher than that of Asians population (Perry et al. 1995). This indicates that the placental weight is genetically determined. Furthermore geographic variations like high altitude also have an influence on placental development (Zamudio 2003), but have not been studied here.

Another focus of this report was to analyze how the gender of the infant and parity influences the placenta weight. Infant birth weight is highly influenced by the gender of the fetus, with an about 3% (119g) higher birth weight for the male fetus (Thompson et al. 2007). Associated with this is an about 1.7% higher placental weight in male than female infants.

Parity also has an influence. Placentas of first pregnancies show a significantly lower weight than placentas of multiparous women. As an explanation remodeling of maternal vascular structure in previous pregnancies offers a more favorable environment for placental development (Bleker et al. 2006).

Multiple pregnancies may also alter placental weight. Multiple pregnancies are relatively uncommon, hence it is more difficult to find information on placental weight throughout a whole pregnancy and only two studies presented such data for twin and triplet placental weight (Pinar et al. 1996, 2002). It is important to emphasise that there can be one placenta mass or several separate placentas in multiple pregnancies. Usually, the whole placental weight is measured. Mean trimmed twin placental weight at term was about 880g i.e. 440g/fetus, while placentas of triplets show a final weight of 1147g i.e. 383g/fetus in the 38th week. Thus, the placental weight per fetus at this time is on average 74g lower in case of a twin pregnancy and in case of a triplet pregnancy 117g lower than in singleton placental weight (Pinar et al. 1996, 2002). A possible explanation for lower placental weights in twin and triplet pregnancies compared to singleton pregnancies is that the neonates of multiple pregnancies are also smaller. There is an association between the infant's size and the placental weight. Small for gestational age infants show

significantly lower placental weights compared to appropriate for gestational age infants. Even 24% lower placental weights were reported for small for gestational age infants compared to infants grown appropriate for gestational age (Heinonen et al. 2001). At the other end of the birth weight range placental weights are higher in infants, who are large for gestational age (Molteni et al. 1978; Bortulus et al. 1998).

In general placental and fetal weight is strongly associated as is reflected by the fetal-placental weight ratio. However, in some situations both weights are differently affected. A mean fetal-placental weight ratio of 7 at term is observed although there are variances depending on the mode of the preparation. The fetal-placental weight ratio is associated with the Apgar score after delivery. Neonates, who are depressed after delivery (Apgar score <6), frequently have a fetal-placental weight ratio >10 (Molteni et al. 1978). On the other hand a low fetal-placental weight ratio is associated with teenage age of the mothers and low fetal weight (Laurie et al. 1999), abnormally high fetal-placental weight ratio compared to fetal weights is also associated with maternal uteroplacental vascular insufficiency like in maternal chronic hypertension, preeclampsia, or major malformations of the fetus. Frequent causes of large placentas are maternal diabetes mellitus, congenital syphilis, Rhesus incompatibility, chronic intrauterine infection, hydrops fetalis and maternal or fetal anemia (Naeye 1987; Pinar et al. 1996).

Maternal nutrition throughout pregnancy is also an important parameter for placental growth and placental weight gain. Maternal nutrient intake during early and late pregnancy was compared and its effect on placental weight was studied. The relation between the intake of energy and the carbohydrates throughout early pregnancy and the placental and birth weight seem to be inverse, i.e. the higher intake the lower placental weight. Moreover increased placental weights were associated with an increased total folate and vitamin C intake in early pregnancy, while in late pregnancy only low carbohydrate intake could be associated with an increase in placental weight.

Other investigators studied the impact of the caloric and the protein/carbohydrate intake during the third trimester. The highest placental diameter reflecting placental weight was described for a caloric intake of 1250-1500 calories/day in the 3rd trimester and a protein/carbohydrate intake ratio between 15-16% (Roseboom 2000).

Mild maternal undernutrition throughout early pregnancy has a positive effect on placental growth, leading to increased placental weight and to a normal ranges birth weights, whereas high energy intake is associated with lower placental and infant birth weights (Huxley 2000; Bortolus et al. 1998). The “Dutch famine” in the Second World

War confirms these findings. During this famine birth weights and placental weights have been well documented. It was observed that undernutrition during pregnancy can influence the placental weight positively as well as negatively. The crucial point is the timing of undernutrition. Reduced energy intake during the first trimester was associated with increasing placental weights, whereas undernutrition through the third trimester led to decreased placental weights and birth weights (Lumey 1998). A possible explanation for this phenomenon is that the placenta, at an early stage of development, is able to cope with such a stressful situation and respond with compensatory placental growth.

This is also seen in women with nausea and vomiting during pregnancy. It usually happens in the first three months and may cause a mild undernutrition. Accordingly, women who experience undernutrition by vomiting show higher placental weights and excellent pregnancy outcomes such as a decreased risk of miscarriage, of perinatal death, lower infants birth weights and preterm birth (Weigel et al. 2006; Huxley 2000). Furthermore the maternal body mass index has an impact on the placental weight. Generally, a high maternal body mass index at booking and throughout pregnancy is positively associated with higher placental weight, while placental undergrowth is frequently associated with low maternal body mass index at booking and throughout gestation (Naeye 1987; Thomson et al. 1968).

Another influencing factor on placental weight seems to be maternal exercise during pregnancy. Performing weight bearing exercise at an intensity of 50% of the maximum preconceptional capacity throughout pregnancy leads to an increase in placental volume as a proxy measure of placental weight. However, the highest average placental weight at term could be observed when the exercise level is decreased in late pregnancy (Clapp et al. 1992, 2000). An explanation for the higher placental volume is that performing regular exercise throughout gestation increases the placental bed blood flow as well as the supply of substrate and oxygen in the long term. Nevertheless, during the exercise the placental bed blood flow decreases which leads to a reduced oxygen and substrate supply (Clapp 2006). It can be assumed that this effect of high intensity exercise on the placenta cannot be compensated by the organism in late pregnancy anymore. This may be the reason for highest placental weights with decreased exercise level in late pregnancy.

In addition to the genetic make up of the fetus a range of maternal factors have an effect on placental development and weight. The placenta should be monitored throughout pregnancy because pathologic changes in placental development will effect fetal growth. Placental weight can serve as an indicator for placental and hence fetal growth.

The following Table 13 offers an overview of influencing factors on placental weight in order to summarize the results of this review.

Table 13: Overview of influencing factors in association with high and low placental weight.

Influences on placental weight	
High placental weight	**Low placental weight**
Preparation	
Untrimmed	Trimmed
Number of the neonates	
Singleton	Twin, Triplet
Gender	
Male	Female
Secular trend	
Current time	Former time
Parity	
Multipara	Primipara
Birth weight category	
AGA, LGA	SGA
Ethnicity	
European	Asian
Maternal nutrition	
Early pregnancy: Low carbohydrate and energy intake High folate and vitamin C intake Late pregnancy: Low carbohydrate intake Maternal undernutrition during the 1st and 2nd trimester High maternal BMI at booking and throughout pregnancy Nausea and vomiting during pregnancy	Early pregnancy: High carbohydrate and energy intake Low folate and vitamin C intake Late pregnancy: High carbohydrate intake Maternal undernutrition during the 2nd and 3rd trimester Low maternal BMI at booking and throughout pregnancy No Nausea and vomiting during pregnancy
Maternal exercise	
Decrease of exercise in late pregnancy	Increase of exercise in late pregnancy

OUTLOOK:

The Placenta has a major influence on the fetal development during gestation and the perinatal outcome. However, the placenta even has the ability to affect offspring development in the long term. For instance infants with low birth weight have an increased risk of postnatal death, birth asphyxia, persistent fetal circulation, meconium aspiration, hypoglycaemia, hypothermia and hypocalcaemia. Furthermore low birth weight seems to be a predictor for diabetes, atherosclerosis, cardiovascular disease, hypertension and stroke later in life (Murphy et al. 2006).

Because of this the placenta should be moved into the focus of research interest. Placental weight estimations during pregnancy by ultrasound may help to assessment of the ongoing pregnancy. To this end new population specific placental weight curves should be worked out in order to have significant marker values that assist detecting pathologic changes as early as possible. Such curves should consider the parity of pregnancies, which definitely influence the placental weight. Furthermore the influence of the infants gender should be taken into account using a large study population.

Especially twin and triplet placental weight curves, which are rare, will get more important in the next few years, because of an increasing number of multiple pregnancies associated with reproductive technologies, for instance in vitro fertilization. Because twin and triplet pregnancies are regarded as high risk pregnancies associated with several of problems they require close surveillance.

Moreover, the society should be informed that maternal nutrition as well as maternal body mass has a major influence on placental and fetal development. These are lifestyle a factors, which are easy to influence at least theoretically.

Other possible placental measures must be considered as well, for instance the placental volume which may also serve as an indicator for pregnancy problems. A small placental volume between the 20th to the 22nd pregnancy week is associated with fetal complications (Wolf et al. 1989).

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