COMPARISON OF CENTRAL CORNEAL THICKNESS AND INTRAOCULAR PRESSURE IN GESTATIONAL DIABETIC ON DIET CONTROL AND NORMAL PREGNANT WOMEN

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Disclaimer

I hereby certify that the work in this dissertation is my own except for the quotations and summaries which have been duly acknowledged.

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ABSTRAK

PENGENALAN

Kehamilan sudah dikenalpasti sebagai salah satu penyebab kepada peningkatan ketebalan kornea sentral serta pengurangan tekanan mata terutamanya waktu penghujung tempoh kehamilan. Namun, tidak banyak data yang diterbitkan berkaitan dengan kencing manis semasa kehamilan yang dikawal melalui pemakanan/diet.

OBJEKTIF

Perbandingan min ketebalan korneal sentral (CCT) dan tekanan mata (IOP) antara wanita mengalami kencing manis waktu mengandung serta dikawal melalui pemakanan, wanita sihat yang tidak mengandung, serta wanita sihat yang mengandung.

KAEDAH

Ini merupakan sebuah kajian perbandingan secara keratan rentas. Seramai 184 wanita telah direkrut, 61 daripadanya merupakan wanita hamil yang menghidap diabetes serta dikawal melalui pemakanan, 63 wanita hamil yang sihat, serta 60 orang wanita sihat yang tidak hamil sebagai subjek kawalan. Kesemua wanita hamil menjalani pemeriksaan mata ketika tempoh kehamilan 36-40 minggu. Pengukuran ketebalan kornea tengah dilakukan dengan menggunakan '*specular microscope'* manakala tekanan mata diukur dengan menggunakan tonometer tanpa-sentuh.

KEPUTUSAN

Statistik memperbandingkan ketebalan min korneal sentral di antara wanita kencing manis waktu mengandung dengan wanita sihat yang mengandung dan tidak mengandung menunjukkan jurang perbezaan min yang ketara ($p<0.05$). Statistik juga membuktikan bahawa tiada perbezaan ketara bagi min tekanan mata (Intraocular pressure) di kalangan ketiga-tiga kumpulan wanita ini.

KESIMPULAN

Perbandingan min ketebalan korneal sentral menunjukkan bahawa wanita mengalami kencing manis waktu mengandung mempunyai min korneal sentral lebih tebal berbanding dengan wanita sihat yang mengandung dan tidak mengandung. Manakala perbandingan tekanan mata (Intraocular pressure) antara ketiga-tiga kumpulan ini menunjukkan tiada perbezaan ketara.

ABSTRACT

INTRODUCTION

Pregnancy is known to cause increase in central corneal thickness (CCT) while reducing intraocular pressure (IOP) especially towards the end of gestation. However there is scarce published data on gestational diabetes on diet control.

OBJECTIVE

To compare the mean CCT and IOP between pregnant women with gestational diabetes (GDM) on diet control, healthy pregnant women and healthy non-pregnant women.

METHODS

This is a comparative cross sectional study. We recruited total of 184 women; 61 pregnant women with GDM on diet control, 63 healthy pregnant women and 60 healthy non-pregnant women as control. All pregnant women undergone once ocular examination during their 36-40 weeks of gestation. CCT measurement was done using specular microscope and IOP measured using non-contact tonometer.

RESULTS

There is statistically significant difference ($p<0.05$) in the mean CCT in women with GDM on diet control when compared to healthy pregnant and healthy non-pregnant women. No significant difference detected in the mean IOP among the groups.

CONCLUSION

GDM women have significantly thicker mean CCT compared to healthy pregnant and healthy non-pregnant women. The level of IOP was similar in all three groups.

Chapter 1
Introduction

INTRODUCTION

1.1. Background

Goldmann applanation tonometer (GAT) is the gold standard in measuring intraocular pressure (IOP) (Busted et al., 1981) and it is the most widely used device for the last half century (Goldmann and Schmidt, 1957). However, IOP obtained using GAT are not without its flaw. It may cause cornea epithelial damage, increased the risk of infection and it requires subjects to have fluorescein or local anesthetic for this procedure (Akar et al., 2005). It is also affected by other factors such as central corneal thickness (CCT), corneal curvature, and axial length (Kohlhaas et al., 2006).

The influence of CCT on IOP has been acknowledge by many investigators, extremes in CCT measurement can leads to over or under estimation of the IOP as GAT was gauged for a CCT of 520 um (Siribunkum et al., 2001). It has been recommended that the GAT readings should be complimented with CCT measurements as CCT measurement can allow for a more accurate estimate of the true IOP.

Newer generation of non-contact tonometers (NCT) has showed extremely reliable and reproducible IOP measurements as the result has compensated for the corneal factors. The advantage of NCT is that it displaces little aqueous, it is quick, does not cause epithelial damage, and doesn't requires any topical ocular medication. Thus reducing the risk of infection and risk of exposure to any drugs especially in pregnant women (Akar et al., 2005).

Pregnancy is characterized by a progressive increase in nutrient-stimulated insulin responses despite an only minor deterioration in glucose tolerance, consistent with progressive insulin resistance. And this changes in carbohydrate and lipid metabolism is to ensure the continuous supply of nutrients to the growing fetus despite intermittent maternal food intake. These changes are progressive and may be accentuated in women who develop gestational diabetes mellitus (GDM) (Butte, 2000).

During pregnancy a huge number of metabolic, hematologic, hormonal and cardiovascular changes occur in a woman body. All tissues of the body, including the eyes are affected during the course of pregnancy. Few studies have showed that in normal pregnancy, the ocular tissues parameters like CCT and IOP has variable changes during different trimester (Efe et al., 2012, Sundaram et al., 2017).

GDM is defined as carbohydrate intolerance that begins or is first detected during pregnancy. It accounts for 90% of cases of diabetes mellitus (DM) in pregnancy. Although most of the women blood glucose level will return back to the normal pre-pregnancy level. A study by Stuebe et al shows that GDM is associated with persistent metabolic dysfunction in women at 3 years after delivery (Stuebe et al., 2011). Various studies also shown that GDM is associated with high risk of development of type 2 DM (Damm, 1998, Fletcher et al., 2002, Greenberg et al., 1995, Kim et al., 2002, Kjos and Buchanan, 1999, Peters et al., 1996). Diabetic retinopathy has never been reported in women with GDM, but pregnant women with pre-existing diabetic will have accelerated progression of diabetic retinopathy.

There is no published study comparing the CCT and IOP changes between women with GDM on diet control and normal pregnancy. Our study focuses on women with GDM who is on diet control and comparing it to normal pregnant women.

This study will provide a baseline data for CCT and IOP in pregnant women and those with GDM. This is important to avoid over and underestimation of increased or low IOP in pregnant situation especially in GDM women.

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Chapter 2
Study Objectives

2. STUDY OBJECTIVES

2.1 General Objective

2.1.1 To evaluate the CCT and IOP between pregnant women with GDM on diet control, healthy pregnant women and healthy non-pregnant women.

2.2 Specific Objective

2.2.1 To compare the CCT between pregnant women with GDM on diet control, healthy pregnant women and healthy non-pregnant women.

2.2.2 To compare the IOP between pregnant women with GDM on diet control, healthy pregnant women and healthy non-pregnant women.

Chapter 3
Manuscript

Comparison of Central Corneal Thickness and Intraocular Pressure in Gestational Diabetes on diet control and normal pregnant women

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3.1. ABSTRACT

BACKGROUND

Pregnancy is known to cause increase in central corneal thickness while reducing intraocular pressure especially towards the end of gestation. However there is scarce published data on gestational diabetes on diet control. We aim to compare the central corneal thickness and intraocular pressure between pregnant women with gestational diabetes on diet control, healthy pregnant women and healthy non-pregnant women.

METHODS

This is a comparative cross sectional study. We recruited total of 184 women; 61 pregnant women with gestational diabetes on diet control, 63 healthy pregnant women and 60 healthy non-pregnant women as control. All pregnant women undergone once ocular examination during their 36-40 weeks of gestation. Central corneal thickness measurement was done using specular microscope and intraocular pressure measured using non-contact tonometer.

RESULTS

There is statistically significant difference ($p<0.05$) in the mean central corneal thickness in women with gestational diabetes on diet control when compared to healthy pregnant and healthy non-pregnant women. No significant difference detected in the mean intraocular pressure among the groups.

CONCLUSION

Gestational diabetes women have significantly thicker mean central corneal thickness compared to healthy pregnant and healthy non-pregnant women. The level of intraocular pressure was similar in all three groups.

KEYWORDS

Gestational diabetes, Diet control, Central corneal thickness, Intraocular pressure, Non-contact tonometer, Specular microscope

3.2. Background

Gestational diabetes mellitus (GDM) is defined as carbohydrate intolerance that begins or is first detected during pregnancy. It accounts for 90% of cases of diabetes mellitus (DM) in pregnancy (Buchanan and Xiang, 2005, Gilmartin et al., 2007, Jovanovic and Pettitt, 2001, Setji et al., 2005)**.** Multiple studies have shown worsening of diabetic retinopathy during pregnancy but GDM does not associate with increased risk of developing diabetic retinopathy(Axer-Siegel et al., 1996, Control and Group, 2000, Klein et al., 1990, Hemachandra et al., 1995, Gabbe and Graves, 2003).

Few studies have reported that in normal pregnancy, the ocular tissues parameters such as central corneal thickness (CCT) and intraocular pressure (IOP) has variable changes during different trimesters(Green et al., 1988, Hørven and Gjønnaess, 1974, Efe et al., 2012, Wilke, 1975, Weinreb et al., 1988, Weinreb et al., 1987). However, so far there is no published study comparing the differences in CCT and IOP measurements between women with GDM on diet control, healthy pregnant women and healthy non-pregnant women. Our study focuses on comparing CCT and IOP measurements between these three groups of women.

3.3. Materials and Methods

This was a cross-sectional study involving 184 pregnant women and 60 healthy non-pregnant women aged 18 to 45 years old; 61 pregnant women who were diagnosed to have GDM on diet control and 63 healthy pregnant women. This study was conducted in the Hospital Universiti Sains Malaysia, Malaysia from January, 01 2015 until February, 28 2017. The study protocol was approved by the Research and Ethics Committee, School of Medical Sciences, Universiti Sains Malaysia, Malaysia and consistent with the tenets of the Declaration of Helsinki.

Pregnant women who is at 36-40 weeks of gestation undergoing routine antenatal checkup at the Obstetrics and Gynecology Clinic of our institution were prospectively enrolled into this study. Inclusion criteria for GDM were pregnant women who had confirmed diagnosis of GDM with the HbA1c level of <6% at all time, aged between 18-45 years. Inclusion criteria for healthy pregnant women were the same age group with absence of concurrent medical problems. Excluded were subjects with known systemic disease or known ophthalmic disorder, contact lenses wearer, refractive error exceeding ± 3.0 diopters and had undergone any type of previous eye surgery. Sixty healthy non-pregnant were staffs or volunteers who accompanied their relatives that came for follow up in our department.

Total of 124 pregnant women who were having an uncomplicated singleton pregnancy were recruited. Every subject was invited for a screening interview during which inclusion and exclusion criteria were assessed. A written informed consent was obtained from all the participants. They underwent further complete ophthalmic examination included best corrected visual acuity, auto-refraction, anterior segment and fundus examinations.

CCT was measured using Topcon SP2000P non-contact specular microscope (Topcon Inc, Itabashi, Tokyo, Japan). It captures the image of the endothelium cells and measures cornea thickness, an average of three consecutive readings was used for data analysis.

IOP was measured using Reichert 7CR (Ametek Inc, Pennsylvania, United States) which is a non-contact tonometer. It utilizes a patented bi-directional applanation process to characterize the biomechanical properties of the cornea and reduce their impact on the IOP measurement. The average of three consecutive readings with acceptable scores (>5) in auto mode was documented for data analysis. All measurements and examinations were performed by the principal investigator of this study with no tropical agent used.

The demographic data, parity, clinical findings, CCT and IOP were documented in a separate data collection sheet. Statistical Package for Social Science (SPSS) version 22 was used to analyses the data. One way anova tests were used to compare the mean of CCT and IOP between pregnant women with GDM on diet control, healthy pregnant women and healthy non-pregnant women.

3.4. Results

All subjects in all three groups are having 6/6 best corrected visual acuity. Anterior segment and fundus examination showed no pathology in all subjects. Table 1 shows the demographic data for the subjects for three groups. The mean age for GDM on diet control group was 32 (4.0) years, 29 (3.0) years for healthy pregnant women group and 27 (5.4) years for healthy non-pregnant women. Most of the subjects were of Malay ethnicity.

We did not find any statistically significant differences between right and left eyes with regards to the variables studied; thus, only the results for the right eye is reported. The mean CCT in GDM on diet control was 552.28 (22.59) μm. While the mean CCT in healthy pregnant women group was 538.75 (22.92) μm and 525.88 (19.31) μm for healthy non-pregnant women. A statistical significant difference ($p<0.05$) was found in the CCT when comparing 3 groups. The central cornea was found to be thickest in GDM on diet control group follow by CCT in the healthy pregnant women group while healthy non-pregnant women has the thinnest CCT.

The mean IOP is significantly lower ($p<0.05$) in both pregnant women groups as compared to the healthy non-pregnant women group. However, there is no statistical significant differences found when comparing the mean between 2 pregnant women groups. The mean IOP in GDM on diet control was 12.92 (2.06) mmHg. And the mean IOP in healthy pregnant women was 12.34 (2.58) mmHg. For the healthy non-pregnant women IOP is 14.20 (2.78) mmHg.

Table 1. Demographic data

		GDM	Healthy Pregnant Women	Healthy non-Pregnant Women
		n=61	n=63	n=60
Mean Age (years) (SD)		32 (4.0)	29 (3.0)	27 (5.4)
Race (n, %)	Malay	60 (98.4)	61 (96.8)	57 (95.0)
	Chinese	1 (1.6)	2 (3.2)	3 (5.0)
Gravida (SD)		2.5 (0.8)	2.3 (0.8)	
Parity (SD)		1.3 (0.8)	1.1 (0.7)	0.5 (0.8)
Gestation (weeks) (SD)		37.9 (1.1)	37.6 (1.1)	
Family history of DM (n, %)	Yes	37 (60.7)	25 (39.7)	18 (30.0)
	No	24 (39.3)	38 (60.3)	42 (70.0)

Table 2.1 Mean CCT in each group

Demographic variables	GDM on diet control	Healthy pregnant women	Healthy non-pregnant women	P value
CCT mean (SD)	552.28 (22.59)	538.75 (22.92)	525.88 (19.31)	0.001

*One way anova, p<0.05 significant

Table 2.2 Post hoc comparison of mean CCT based on GDM on diet control group

Demographic variables	N	Mean difference (95%CI)	F-statistics (df1, df2)	P value
Mean CCT			22.398 (2,181)	
GDM-Healthy pregnant	61	13.53 (3.91,23.15)		0.002
GDM-Healthy non-pregnant	63	26.40 (16.66,36.13)		0.001
Healthy pregnant-Healthy non pregnant	60	12.86 (3.20,22.52)		0.003

*One way anova, p<0.05 significant

Table 3.1 Mean IOP in each group

Demographic variables	GDM on diet control	Healthy pregnant women	Healthy non-pregnant women	P value
IOP mean (SD)	12.92 (2.06)	12.34 (2.58)	14.20 (2.78)	0.000

*One way anova, p<0.05 significant

Table 3.2 Post hoc comparison of mean IOP based on GDM on diet control group

Demographic variables	Mean difference (95%CI)	N	F-statistics (df1, df2)	P value
Mean IOP			8.883 (2,181)	
GDM-Healthy pregnant	0.58 (-0.53,1.68)	61		0.401
GDM-Healthy non-pregnant	-1.28 (-2.40,-0.16)	63		0.015
Healthy pregnant-Healthy non pregnant	-1.86 (-2.97,-0.75)	60		0.001

*One way anova, p<0.05 significant

3.5. Discussion

In this hospital-based sample, we present a new data on CCT and IOP in GDM women who is on diet control. Diabetes has been associated with increased CCT in multiple published studies(Siribunkum et al., 2001, Busted et al., 1981). Busted at el noted that increased CCT present very early in the disease and maybe one of the earliest changes detectable in diabetic eye. Multiple previous published studies have studied the CCT and IOP changes during normal pregnancy and have shown that CCT increases with reciprocal drop in IOP during the course of pregnancy especially towards term. Three months post-partum, both CCT and IOP will returned to the pre-pregnancy state(Hørven and Gjønnaess, 1974, Weinreb et al., 1988, Qureshi et al., 2000, Phillips and Gore, 1985). This study differs from others as we compared CCT and IOP between pregnant women with GDM on diet control, healthy pregnant women, and healthy non-pregnant women.

Table 4 summarizes various published study done on healthy pregnant women and non-pregnant women. However, we noticed that so far there is no published data regarding CCT and IOP changes in GDM patients. In our data we noticed that ours are parallel with reports from other countries in which the CCT increased with reciprocal drop in IOP in the third trimester. We also have look into whether gravidity, parity, weeks of gestation and family history of diabetes would be affecting our objectives and found that there is no significant association of these factors with CCT and IOP ($p>0.05$).

Table 4 Comparison of CCT and IOP during third trimester of healthy pregnant women and healthy women in previously published data

	Present Study (2017)			Akar et al. (2005)		Hashemi et al. (2010)		Goldich et al. (2011)		Efe et al. (2012)		Sundaram et al. (2017)	
Country	Malaysia			Turkey		Iran		Israel		Turkey		India	
	GDM	Pregnant	Non-pregnant	Pregnant	Non-pregnant	Pregnant	Non-pregnant	Pregnant	Non-pregnant	Pregnant	Non-pregnant	Pregnant	Non-pregnant
Groups (n)	61	63	60	72	74	NA	33	NA	22	25	NA	100	NA
Age mean (SD)	32 (4.0)	29(3.0)	27(5.4)	25.4(2.3)	26.1(2.1)	NA	28.6(2.6)	NA	19.5(1.5)	29.0(3.0)	NA	25.0(3.9)	NA
CCT	549.4(24.2)	537.0(24.2)	532.8(25.9)	NA	NA	NA	533.0(29.0)	NA	540.0(41.0)	573.7(24.0)	NA	552.8(41.3)	NA
CCT Method	Specular microscope			NA	NA	NA	USG	NA	USG	USG	NA	USG	NA
IOP	12.9(2.1)	12.3(2.6)	14.2(2.8)	13.7(2.3)	14.1(2.1)	NA	NA	NA	14.5(3.5)	14.4(2.1)	NA	11.1(1.1)	NA
IOP Method	NCT			NCT		NA	NA	NA	GAT	NCT	NA	GAT	NA

NA: Not available

As noted in our Table 1, our demographic data is consistent with the report from Coustan at el who recruited 6034 women for a population based study on maternal age and screening for GDM. He noted that there was some increasing likelihood of GDM with increasing maternal age(Coustan et al., 1989). Our study showed that CCT is thicker in women with GDM on diet control. We hypothesis that the increased CCT observed in pregnant women with GDM on diet control is associated with hyperglycemia rather than advancing age, as CCT is independent of age(Su et al., 2008).

We observed thicker mean CCT in healthy pregnant lady as compared to healthy non-pregnant women ($p<0.001$). However, we cannot compare this finding to the published data as there is no published data of similar design. Efe et al and Sundaram et al has reported CCT and IOP in healthy pregnant women only(Efe et al., 2012, Sundaram et al., 2017). On the other hand, Hashemi et al and Goldich et al has published data on CCT and IOP in healthy non-pregnant women only(Goldich et al., 2011, Hashemi et al., 2010).

IOP measurement using Goldmann applanation tonometer (GAT) has been known to be affected by CCT, a thicker corneal will give a falsely higher value, vice versa. Although increasing evidence suggests that other tonometers share this similar problem, the non-contact tonometer (NCT) is found to be the most stable and able to get reproducible measurement(Akar et al., 2005).

In our study, we found that IOP is statistically significant lower in 2 pregnant groups when compared to healthy non-pregnant women. However, IOP shows no statistical significant between women with GDM on diet control and normal pregnant women. During second and third trimester of pregnancy where the CCT is the greatest, a paradoxical state occurs as the IOP measurements at this stage tends to be lower. The ocular hypotensive effect of pregnancy has been reported by many authors and they suggested that primary or secondary increases in outflow facility is the reason behind.(Green et al., 1988) Other study shows that estrogen increased thickness and reduced stiffness in rodent eye (Spoerl et al., 2007). Ziai et al suggests that excess progesterone during pregnancy acts as glucocorticoid receptor antagonist and this blocks the ocular hypertensive effect of endogenous steroids (Ziai et al., 1994).

Measurement of IOP using GAT will be affected by variation in CCT as GAT was gauged for a CCT of 520 um (Tonnu et al., 2005). In our study, the increased CCT in women with GDM on diet control has no significant effect on the IOP. We postulate that because newer generation of NCT has better ability in removing corneal factors affecting IOP measurement, however this will need further clinical study to come to conclusion. Nevertheless, by reducing the risk of infection and exposure to any drugs especially in pregnant women, NCT will be a better alternative for IOP measurement(Jorge et al., 2002, Akar et al., 2005).

We studied CCT and IOP changes between 36 to 40 weeks of gestation in view that multiple published studies has noticed that during this period CCT and IOP has the most dramatic changes as compared to other period of gestation (Akar et al., 2005, Efe et al., 2012, Qureshi et al., 1996). Another reason behind is because GDM is only diagnosed during 24-28 weeks of gestation. Further study would definitely be needed to look for the variability of these measurements in one patient during the course of pregnancy.

3.6. Conclusion

GDM women have significantly thicker mean CCT compared to healthy pregnant and healthy non-pregnant women. The level of IOP was similar in all three groups.

3.7. Acknowledgements

We would like to thank all the faculty members of Department of Ophthalmology and Department of Obstetrics and Gynecology in Hospital Sultanah Aminah Johor Bahru (HSAJB) and Hospital Universiti Sains Malaysia (HUSM) for extending their help and support in my data collection.

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3.9. Authors' contribution

KKW carried out the study, interpreted and analysed the data, and prepared the manuscript. SI designed the study, corrected the manuscript and monitored the progress of research.

3.10. Competing interest

All authors have no competing interest in this study.

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