REPRODUCTION AND BIRTH CONTROL AMONG DIABETIC WOMEN

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COMMITTEE DECISION

This thesis (Reproduction and Birth Control among Diabetic Women) was successfully Defended and approved on 3-6-2008

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تعتمد كلية الدراسات العليا
هذه النسخة من الرسالة
التوقيع.....التاريخ.....

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DIDICATION

To

My family

My father and mother for their great love and support.

My brothers and sisters for their great love.

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LIST OF ABBREVIATION

ADA : American Diabetes Association

COC: combined oral contraceptive

C/S: Caesarean Delivery

FSH: Follicular Stimulating Hormone

GDM: gestational diabetes mellitus

GNRH: Gonadotropin Releasing Hormone

HCG: Human Chorionic Gonadotropin

HCS: Human Chorionic Somatotropin

HPL: Human Placental Lactogen

IDM: Infant of Diabetic Mother

IGT: Impaired Glucose Tolerance

IUFD: Intra Uterine Fetal Death

IUD: Intra Uterine Device

LH: Luteinizing Hormone

MSAFP: Maternal Serum α Feto Protein

MOH: Ministry Of Health

NCDEG: National Center for Diabetes, Endocrinology, and Genetics

PGDM: Pregestational Diabetes Mellitus

US: Ultra Sound

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ABSTRACT

To compare reproductive health history, pregnancy outcomes, birth control and family planning practices among diabetic and non-diabetic women in reproductive age group.

Comparative study was carried out on a sample of 1500women. They were divided into two group's 750 married fertile diabetic, and cooperative women (type1, or type2, or gestational diabetes mellitus) versus 750 healthy non-diabetics, and cooperative women. During the period from September 2007 to January 2008, data were collected using structured interview.

The mean age of menarche was13.3in diabetic women and 13.4 in non-diabetic women (p=0.06), was not statistically significant. The congenital malformation rate was significantly higher in diabetic women than non-diabetic women (4.9%, and 1.1%

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respectively). The stillbirth, neonatal death, and intra uterine fetal death rates were also higher in diabetic women (8.9%, 7.1%, and 3.5% respectively) than non diabetic women (2.7%, 1.5%, and 1.7% respectively). And the same was true for macrosomia 40.2%for diabetic women and 4.2%for non diabetic women. The rate of neonatal hypoglycemia in diabetic women was 20.7%. Preterm delivery was found1.9 times higher in diabetic women (15.5%) compared with 6.1% of non-diabetic women, ($p<0.005$). Caesarean delivery was significantly more frequent in diabetic women than non-diabetic women (29.6%, 15.5%respectively). The most common method used for family planning after the last pregnancy was intra uterine device in both groups while tubal legation was used in diabetic women more than non diabetic women. Breast-feeding among diabetic women was less than non diabetic women (p value < 0.005).

Adverse pregnancy outcomes in diabetic women remain high compared with non-diabetic women. Diabetes was found to be independently associated with serious adverse outcomes in pregnancy compared with non-diabetic women. Intra uterine device was the most common method used for family planning in both diabetic and non-diabetic women. There is a need to increase awareness about the importance of preconception care, planning pregnancy, family planning method, and breast-feeding among diabetic women.

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Chapter One

INTRODUCTION

Diabetes is the most chronic prevalent medical condition affecting the reproductive health. It is associated with adverse pregnancy outcome [1]. A nation wide population-based survey in the United States revealed that nearly 4 percent of pregnant women have diabetes: 88 percent had gestational diabetes mellitus, defined as glucose intolerance that appeared during pregnancy, whereas 12 percent were women known to have diabetes. Of those with pregestational diabetes, 35 percent had type 1 and 65 percent type 2 diabetes [2]. Pregestational diabetes mellitus represents one of the most challenging medical complications of pregnancy. More than 8 million women in the United States have pre gestational diabetes mellitus, and it is observed in 1% of all pregnancies [3, 4, 5]. Although 90%of diabetic cases encountered during pregnancy are gestational diabetes mellitus (GDM), more than one-half of those women eventually develop type 2 diabetes mellitus later in life.

The prevalence of type 2 diabetes in young women and children is increasing: WHO data from 1992 showed that the prevalence of diabetes in women of childbearing age (20-39) to be highest in native Americans, Micronesians, Rural Fijians, and Aboriginal Australians, in whom the populations have very high rate of type 2 diabetes [6]. In adolescents, type 2 diabetes has been increasingly noted in native Canadian and American populations, Mexican- Americans, African – Americans , Japanese people , and Libyan Arabs[7] . The prevalence of diabetes in developing countries, such as the Arab countries, varies from 3%in Sudan to 35%in Bahrain [8]. In a recent study [9] in Jordan, the age-standardized prevalence of diabetes mellitus (DM) and impaired glucose tolerance (IGT) were 17.1 and 7.8%respectively, confirming

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that the prevalence of diabetes and IGT is high in Jordanians and increasing. This rise in the prevalence of type 2 diabetes in general, and in younger people in particular, has led to an increasing number of women with type 2 diabetes in pregnancy.

Several studies [10,11,12] have confirmed that outcomes of pregnancy in women with both type 1 and type 2 diabetes remain poor compared with women without diabetes, and that outcome is frequently related to poor glycemic control in early pregnancy because hyperglycemia leads to dysmorphogenesis. It is also known that excess glucose metabolism by embryos in a hyperglycemic environment disturbs a complex network of biochemical pathways [13].Women with diabetes face unique health challenges throughout their life cycle. Diabetes can have a significant impact on puberty, menstruation and reproduction [14].

Puberty

Menarche: Is the occurrence of the first menstruation, may occur as early as age nine or as late as seventeen year and still be within normal limits [15]. In type1 diabetes, the age of menarche is delayed by one year when compared to control group [16] and women with type1 diabetes had more menstrual problems (long menstrual cycle, menorrhagia) and other reproductive consequences [17]. Study conducted by Squib et al in 2005, found that the late age at menarche in type 2 diabetes mellitus and abnormal glucose tolerance was inversely associated with fasting and post challenge glycemia [18].

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Pregnancy outcomes

Spontaneous Abortion: - The increased frequency of spontaneous abortion in poorly controlled diabetic women is thought to be secondary to hyperglycemia, maternal vascular disease, including uteroplacental insufficiency, and possibly immunological factors [19, 20, 21]. The excess risk of spontaneous abortion in diabetic women is probably related, in part to an increased frequency of dysmorphogenesis [13].

Perinatal Mortality: - Remains significantly elevated in women with pregestational diabetes compared to the background population [22, 23]. A threefold increase in perinatal mortality has been reported in women with type 2 diabetes compared to women with type 1 diabetes [12].

Major Congenital Malformations: Considered the leading cause of mortality and serious morbidity in infants of mothers with type 1 or type 2 diabetes [10]. Clinical trials of preconception care to achieve stringent blood glucose control in the preconception period and during the first trimester of pregnancy have demonstrated striking reductions in rates of malformations compared with infants of diabetic women who did not participate in preconception care [24]. The critical time for optimal glycemic control is before 7 weeks' gestation, during early organogenesis [25].

Macrosomia: Maternal diabetes mellitus significantly increases the chance of having a macrosomic infant; it also changes the anthropomorphic measurements of infants of diabetic mothers compared to offspring of non-diabetic women [26]. Macrosomia is defined as fetal weight greater than 4.0 kg or birth weight above the 90th percentile for gestational age [27]. Macrosomic infants of diabetic mothers have larger shoulder

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and extremity circumferences, a decreased head-to-shoulder ratio, higher body fat, and thicker upper extremity skin folds compared to non-diabetic control infants of similar weight and length [26]. These changes are temporary and caused, at least in part, by increased maternal-fetal transfer of substrates (glucose, amino acids) leading to fetal hyperinsulinemia [28]. Although macrosomia is typically considered a late pregnancy/neonatal problem, the pathogenetic factors leading to macrosomia appear to be present in early pregnancy [29].

Neonatal Hypoglycaemia: defined as blood glucose levels below 40 mg/dL (2.2 mmol/L) [30]. Hypoglycemia is most common in macrosomic infants; this incidence is related to persistent hyperinsulinemia in the newborn after interruption of the intrauterine glucose supply from the mother. A potentiating factor is the depressed response to hypoglycemia of counter regulatory hormones, such as glucagon and catecholamine, in infant of diabetic mothers [31, 32]. Strict glycemic control during pregnancy decreases but does not abolish the risk of neonatal hypoglycaemia [33], as illustrated in a report of 78 type 1 diabetics rigorously managed during pregnancy: 14% of the newborns had hypoglycemia [34]. Infant of diabetic mothers who are premature or small for gestational age (SGA) are also at increased risk of hypoglycemia because glycogen stores are reduced and hyperinsulinemia decreases the ability to mobilize hepatic glycogen [35].

Route of Delivery: - Maternal diabetes alone is not an indication for caesarean birth in the absence of usual obstetric indication. Excessive fetal growth among women with diabetes may be considered an indication for caesarean delivery due to the risk of morbidity from shoulder dystocia [36, 37]. It has been suggested that neonates with shoulder dystocia have greater shoulder and chest –to head disproportion than

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macrosomic infants without this complication [38]. For these reasons, the position of American college of obstetricians and Gynaecologists is that, although the diagnosis of macrosomia is imprecise, prophylactic caesarean delivery may be considered to prevent brachial plexus injury when the estimated fetal weight is greater than 4500g in women with diabetes [39].

Birth Control

Despite the seriousness and risk of pregnancy related complications, two thirds of women with diabetes have not received preconception counselling, with rates of unplanned pregnancies between 43%and 78% [10, 40, 41] . Planned pregnancies are the core of family planning. There are several options of contraception for women with diabetes, with each providing benefits and some posing risks [42]. Criteria for selection should include safety and effectiveness and should be individualized for each woman's situation [10]. Reliable contraception is particularly important for diabetic women as unplanned pregnancy in these patients is associated with an increased risk of spontaneous abortion and congenital malformations if glycemia is not well controlled. Barrier methods are not as reliable as other methods because diabetic women are more likely to have menstrual irregularities and liability to infections [17].

Better methods of birth control for diabetic women include the following:

Oral contraceptives are highly effective in preventing pregnancy for diabetic women. Estrogen doses of ≤35 mcg have no effect on carbohydrate metabolism, plasma glucose, or insulin sensitivity; estrogens also increases HDL and total cholesterol and decreases LDL cholesterol [43]. On the other hand, progestin's increase peripheral insulin resistance, lower HDL cholesterol, and increase LDL cholesterol; the

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magnitude of these changes depends on the preparation. Other estrogens-progestin preparations appear to have similar effects, but have not been extensively studied in diabetes [44]. The lowest dose of estrogen and progestin should be prescribed to minimize the risk of complications. The American College of Obstetricians and Gynaecologists recommends; based on theoretical concerns, the use of combined oral contraceptives limited to diabetic women who do not smoke, are younger than 35 years of age, and are otherwise healthy (i.e., without evidence of hypertension, nephropathy, retinopathy, or other vascular disease) [39]. American Diabetes Association guidelines state that the selection of a method of contraception for an individual patient should be based on the same considerations that apply to women without diabetes [10]. Intrauterine devices (IUD) (e.g., copper T380 IUD or levonorgestrel-releasing IUD) are as safe and effective as for non diabetic women [45]They are a good alternative for women with microvascular disease who may be at higher risk for cardiovascular complications from oral contraceptives. Diabetic women are at increased risk for developing endometrial cancer; use of the levonorgestrel-releasing IUD should be protective against development of endometrial hyperplasia (the precursor to endometrial cancer) and may reduce this risk).

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Breast-Feeding

Has been shown to protect against the development of insulin dependent diabetes mellitus [46]. Owen CG found that breastfeeding in infancy is associated with a reduced risk of type 2 diabetes, with marginally lower blood glucose and serum insulin concentrations in infancy [47]. Breastfeeding [48] is good for both mother and her baby as it lowers the baby's risk of getting diabetes, and in the same time, it is useful to the mother to lose weight between pregnancies and help her body to use insulin in better way and help to prevent obesity of her body.

The importance of this study stems from high percent of poor pregnancy outcomes in diabetic women. In addition, no previous studies conducted on diabetic Jordanian women. Another goal of our study is to identify the practices of diabetic women regarding birth control and breast-feeding.

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OBJECTIVES

1 -To compare reproductive health history, birth control and family planning practices among diabetic and non-diabetic women in reproductive age group.

2 -To compare pregnancy and birth outcomes history among diabetic and non-diabetic women in reproductive age group.

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Physiology of Reproduction

Female reproductive cycle: can be defined as episodic uterine bleeding in response to cyclical hormonal changes. It is the process that allows for conception and implementation of new life. The purpose of menstrual cycle is to bring an ovum to maturity and renew a uterine tissue bed that will be responsible for its growth should it be fertilized [(49)].

Hormonal Regulation of Female Reproductive Cycle

During their reproductive years, non pregnant females usually experience a cyclical sequence of changes in their ovaries and uterus. Each cycle takes about one month and involves both oogenesis, the process of formation and development of oocyte, and preparation of the uterus to receive a fertilized ovum. Hormones secreted by the hypothalamus, anterior pituitary gland, and ovaries control the principal events. The menstrual cycle is a concurrent series of changes in the endometrium of the uterus to prepare it for the arrival of a fertilized ovum that will develop in the uterus until birth. If fertilization does not occur, the lining (stratum functionalis) of the endometrium is shed during menstruation. The general term female reproductive cycle encompasses the ovarian and uterine cycles, the hormonal changes that regulate them, and also the related cyclical changes in the breasts and cervix [(50)]. The ovarian and uterine cycles are controlled by chemical messengers or hormones. Gonadotropin releasing hormone (GnRH) is secreted by the hypothalamus and stimulates the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the anterior pituitary gland. FSH, in turn, initiates follicular growth and the secretion of estrogens by the growth follicles. LH stimulates the further development of ovarian follicles and their full secretion of estrogens, brings about ovulation, promotes formation of the corpus

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luteum and stimulates the production of estrogens, progesterone, relaxin and inhibin by the corpus luteum [51]. Estrogens are hormones having several important functions. They promote the development and maintenance of female reproductive structures, secondary sex characteristics and the breasts. The secondary sex characteristics include the distribution of adipose tissue in the breasts, abdomen, and hips; also voice pitch, a broad pelvis and the pattern of hair growth on the head and body. Estrogens increase protein anabolism and lower blood cholesterol level. Moderate amount of estrogens in the body inhibit both the release of GnRH by the hypothalamus and secretion of LH and FSH by the anterior pituitary gland. At least six different estrogens are present in the plasma of human females but only three are present in significant quantities: B-estradiol, estrone, and estriol. In nonpregnant females, the principle estrogen is B-estradiol, which is synthesized from cholesterol in the ovaries [69]. Progesterone is secreted mainly by cells of the corpus luteum and acts synergistically with estrogens to prepare the endometrium for the implantation of a fertilized ovum and the mammary glands for milk secretion. High levels of progesterone also inhibit the secretion of GnRH and LH. A small quantity of the relaxin hormone produced by the corpus luteum during each cycle, relaxes the uterus by inhibiting contractions. This is probably facilitates the implantation of an ovum which is perhaps more likely to occur in a relaxed uterus. During pregnancy, the placenta produces much more relaxin and continues to relax the uterine smooth muscle. At the end of pregnancy, relaxin also increases the flexibility of the symphysis pubes and may help dilate the uterine cervix, both of which ease delivery of the baby. Inhibin is secreted by granulose cells of growing follicles and by the corpus luteum of the ovary. It inhibits secretion of FSH and to a lesser extent, LH [51].

Phases of Female Reproductive Cycle: The duration of the reproductive cycle is

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divided into four phases: the menstrual phase, the preovulatory phase, ovulation, and the postovulatory phase. The menstrual phase lasts for about five days and by convention the first day of menstruation marks the first day of a new cycle. The endometrium is shed and the discharge occurs because the declining levels of hormones, especially progesterone, stimulating the release of prostaglandins that cause the uterine spiral arterioles to constrict. As a result the cells they supply become oxygen deprived and die and the stratum functionalis sloughs off. During this phase, some 20 secondary follicles in each ovary begin to enlarge and continue to do so through the preovulatory phase, the time between menstruation and ovulation, under the influence of FSH. By about day six, one follicle has outgrown the others and becomes the dominant follicle. Estrogens and inhibin secreted by the follicle decrease the secretion of FSH and the other follicles stop growing. The mature dominant follicle, or Graafian follicle, continues to enlarge until it is ready for ovulation. It continues to produce estrogen under the influence of LH. At day 14, the follicle ruptures and releases an oocyte into the pelvic cavity. This process is known as ovulation. After ovulation the mature follicle collapses [(50)]. The postovulatory phase of the female reproductive cycle is the most constant in duration, lasting approximately from day 15 to 28 and represents the time between ovulation and the onset of the next menses. In the ovary, after ovulation, the LH stimulates the remnants of the mature follicle to develop into the corpus luteum, which secretes increasing quantities of progesterone and some estrogens. This is called the luteal phase of the ovarian cycle. Subsequent events in the ovary that ovulated an oocyte depend on whether or not the oocyte becomes fertilized. If the oocyte is not fertilized, the corpus luteum has a lifespan of only two weeks, after which it degenerates into a corpus albicans. As the levels of progesterone, estrogens, and inhibin decrease during this phase, GnRH, FSH, and LH release increases because of the lack of feedback suppression by the ovarian

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hormones. Then follicular growth resumes and a new ovarian cycle begin [50]. However, the oocyte is fertilized and begins to divide; the corpus luteum persists past its normal two-week lifespan. It is prevented from degenerating by the human chorionic gonadotropin (HCG), a hormone produced by the chorion of the embryo as early as eight to 12 days after fertilization. HCG acts like LH in stimulating the secretory activity of the corpus luteum and the presence of HCG in maternal blood or urine is an indicator of pregnancy [50].

Pathophysiology of Diabetes in Pregnancy

Pregnancy is characterized by a complex endocrine-metabolic adaptation process including impaired insulin sensitivity, increased β-cell response, moderate increase in blood glucose levels particularly following the ingestion of a meal, and changes in the levels of circulating free fatty acids, triglycerides, cholesterol, and phospholipids. These changes do not reflect a pathological condition; rather, they represent a necessary, possibly indispensable, adaptation to meet the energy demand of the fetus and to prepare the maternal organs for delivery and lactation [52]**.** During the first trimester of pregnancy, insulin sensitivity is normal if not higher than normal [53]. As pregnancy progresses, a condition of insulin resistance sets in, the impairment of insulin action being more pronounced at the level of skeletal muscle than adipose tissue [54]. The reduction of insulin sensitivity is a common event and is independent of the initial condition. Catalano et al [55] using the euglycemic-hyperinsulinemic clamp, estimated a 47% reduction in insulin sensitivity in obese women and a 56% reduction in normal-weight women in the third trimester of gestation. According to other studies, with the progression of pregnancy, insulin sensitivity can be reduced as much as 60 to 80% [56]. The insulin resistance developing in pregnancy is likely to be

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a physiological event favouring glucose supply to the fetus. The reduced insulin-mediated utilization of glucose switches the maternal energy metabolism from carbohydrates to lipid substrates (free fatty acids), redirecting carbohydrates toward the fetal tissues [56]. Even the slight, though prolonged, postprandial hyperglycemia associated with impaired insulin sensitivity can contribute to rerouting nutrients from the mother to the fetus [57]. The increase in insulin resistance is largely result of mixture of placental hormones, including estrogens, progesterone, cortisol, human chorionic somatotropin (HCS) or human placental lactogen (HPL), and GH [57]. Estrogens and progesterone increase during the early phase of pregnancy and are involved in maternal glyco-metabolic modifications. Estrogens increase insulin concentration and insulin binding [58], while progesterone causes glucose intolerance by decreasing insulin binding and glucose transport, and by impairing insulin suppression of hepatic gluconeogenesis [58]. Plasma concentration of cortisol approximately doubles during pregnancy. An excess of glucocorticoids can induce insulin resistance at a post receptor level by impairing insulin receptor phosphorylation and by reducing the cell content of IRS-1 [59]. The hormone human placental lactogen (HPL) is the product of the hPL-A and hPL-B genes. It is secreted into the maternal and fetal circulations after the sixth week of pregnancy. HPL promotes maternal production of insulin-like growth factors (IGFs), modulates intermediary metabolism, and contributes to directing energy substrates toward the fetus [60]. Similar to the growth hormone, HPL contributes to the reduction of insulin sensitivity [58] hPL has been suggested to play a role in the control of embryonic growth [61]. Finally, lactogen hormones (HPL, GH, and PRL) have been implicated in the regulation of islet mass increase that occurs during normal pregnancy [62]. In

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normal pregnancies, glucose homeostasis is maintained, in spite of insulin resistance,

by a concomitant compensatory increase in insulin secretion. The increase in insulin secretion is associated with hypertrophy and hyperplasia of the β-cells [62]. It is very likely that these changes are triggered and maintained by placental hormones. Inadequate β-cell adaptation is likely to contribute to the development of gestational diabetes. In ability to compensate for insulin resistance may reflect intrinsic alterations of the β-cell, as in the case of glucokinase mutations (5% of all cases of GDM) [63], or extrinsic mechanisms, as in the case of an autoimmune process (<10%). However, the vast majority of the cases do not recognize an identifiable cellular alteration. Both in GDM and type 2 diabetes, intolerance to carbohydrates develops as soon as β-cell secretion is no longer sufficient to compensate for insulin resistance [64]. Glucose crosses the placenta by facilitated diffusion therefore; the concentration in maternal blood determines the level in the fetus. Insulin does not cross the placenta. In the second trimester, maternal hyperglycemia produces fetal hyperglycemia, causing stimulation of the fetal ß cells and fetal hyperinsulinemia. Insulin is the major fetal growth hormone and produces excessive fetal growth particularly in fat, the most insulin-sensitive tissue. The fetus of the poorly controlled diabetic mother is not only more likely to weigh more than 4000 gm but to be disproportionately large about the shoulders and chest, more than doubling the risk for shoulder dystocia at vaginal delivery. These large fetuses are also at greater risk for intrauterine fetal death during the last 4–6 weeks of gestation [65].

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Chapter Two

LITERATURE REVIEW

Puberty

Findings of the effect of diabetes on the age at menarche have been inconsistent, some clinical studies and retrospective analysis have found delays [16, 66], whereas other studies have found normal age at menarche [67, 68]. The Wisconsin Diabetes Registry Project[69], which is population based incident cohort of individuals with type1 diabetes, found that age at menarche was moderately delayed by approximately 3 months in young women with type 1diabetes as compared with the over all united states population. A study conducted in 1997, showed that the children with insulin dependant diabetes mellitus have normal onset of puberty [70]. A study conducted by Saquib et al in 2005, found that the late age at menarche in type 2 diabetes mellitus and abnormal glucose tolerance was inversely associated with fasting and post challenge glycemia. [71]. A study conducted in Denmark in 1992 showed the age of menarche among women having developed insulin dependent diabetes mellitus before age of 10 years was delayed by one year when compared to control [16]. Another study conducted in 2003 [17], to evaluate menstrual cycle histories among women with type 1 diabetes and control women without diabetes showed that women with type 1had more menstrual problems (long cycle and long menstruation) than control group.

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Pregnancy Outcomes

Major Congenital Malformations: Several UK studies [72, 73, 74] reported that congenital malformation in type 1diabetes were several times greater than the background population. A cross sectional study was conducted in 12 perinatal centers in France in 2000-2001 among 435 pregnant diabetic women, the result found that the rate of congenital malformation was 4.1 % [75]. A study conducted in North West England showed that the infant of women with pre-existent insulin dependant diabetes mellitus have a10 fold greater risk of congenital malformations[72]. Another study performed by Hawthorne LM, found that [22] congenital malformation is four times higher for pregnancies in diabetic women than for those in women who do not have diabetes. Kucera found that the offspring of diabetic pregnancies have a 2-3fold greater chance of having a congenital anomaly as compared with infants of non-diabetic mothers [76]. Miller and co-workers [77] at the Joslin Clinic in a retrospective study correlated the incidence of major malformations among offspring of diabetic women with maternal HBA_{1c} concentrations of less than 6.9% and who were deemed to be in excellent metabolic control produced no infants with congenital malformations. Women with HBA_{1C} concentrations ranging from 7.0% to 8.5% had a 5.1 % malformation rate, and those with values greater than 8.6% had a 22.4% major malformation rate. A study conducted by Lapolla A et al [78], reported that congenital malformation was (4.9) in diabetic women more than non-diabetic Italian women (0.86). A study conducted by Galindo et al [79], showed that 13.4% of offspring of pregestational diabetic women who had congenital malformation. Another study conducted in India [80] reported that the prevalence of congenital malformation 3.8%among PGD, 1.4% in GDM and 0% among non-diabetic women.

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A nation population based study [81] to compare pregnancy outcomes in patients with type1 diabetes with back ground population. The result found that the congenital malformation rate was 5% in the diabetic women and 2.8% in the background population.

Perinatal Mortality: Prospective study conducted in 33centers in Italy [78] to determine pregnancy outcomes in diabetic women, the result found that stillbirth is higher in diabetic women than non diabetic women (1.26%vs0.30%), and the neonatal death rat of 0.63% in Italian diabetic women where it is 0.32% in non diabetic women. Cuddy T [82] found the perinatal mortality in type 2 diabetes mellitus was 46.1/1000, significantly higher than the rates for the general population (12.5/1000). Cohort study conducted in England, Wales and Northern Ireland between 1st of march2002 and 28th of February 2003, involved 2359 pregnant women with diabetes. It showed that perinatal mortality in babies of women with diabetes was31.8/1000 births, and was nearly four times higher than that in the general population [83]. Prospective multi center study took place in eight Danish centers treating pregnant women with type1 diabetes during 1993-1999, to compare pregnancy outcome in type1 diabetes with background population; the result showed that the perinatal mortality rate was 3.1% in type1diabetic women compared with 0.75in the background population [84]. Dudley DJ found that stillbirth is associated with hyperglycemia, resulting in fetal anaerobic metabolism with hypoxia and acidosis. Prevention of stillbirth in women who have diabetes hinges on intensive multidisciplinary perinatal care with control of blood sugars [85]. Study performed by Dos Santos Silva et al, [86] found that the rate of stillbirth, and neonatal death are

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higher than the general population (2.5, 1.2%respectively).

Spontaneous Abortion: A study was conducted by Galindo et al [79], showed that 7.9% of pregestational diabetic women had spontaneous abortion**.** Another study conducted in North West England showed that the rate of spontaneous abortion was 17% in women with pre-existent insulin dependant diabetes mellitus [72]. Shefali AK et al [80] reported that the proportion of spontaneous abortion was 10.1%in pregestational diabetes mellitus, 2.7% in gestational diabetes mellitus, and 0%in non-diabetic controls.

Macrosomia: Cohort study with a numbers of 516 infants of diabetic mothers and 150,589 infants of non-diabetic mothers from singleton pregnancy were studied. Infants of diabetic mothers had significantly higher rates of large for gestational age birth than infants of non-diabetic mothers [87]. Deborah L. Coney(2002), found that the macrosomic infant of diabetic mothers[88] had more than 3 fold higher risk of shoulder dystocia than macrosommic infant of non diabetic mothers(14.7%vs.4.4%), part of this increased risk can be attributed to higher macrosomia rate among diabetic women as compared to normal women. Ballara et al (1993) studied 170 infant of diabetic mothers and 510 of non-diabetic mothers matched for gestational age, race, and years of delivery. 45% of infant of diabetic women had macrosomia compared with 8%of control infants [89]. Prospective study was designed to characterize the macrosomic neonate anthropometrically. The results revealed that neonates experiencing shoulder dystocia had significantly greater shoulder-to-head and chest-to-head disproportions than did macrosomic neonates delivered by caesarean section for failed progress in labour or macrosomic neonates delivered without shoulder

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dystocia.

In addition, neonates of diabetic mothers also showed significantly greater shoulder-head and chest-head size differences than did neonates of non-diabetic mothers of comparable weight [90]. A study conducted in India [80] reported that the prevalence of macrosomia is 19.2% among PGD, 27.6%inGDM and 7.1% among non-diabetic women.

Neonatal Hypoglycaemia: Roy Taylor found that neonatal hypoglycaemia correlates with maternal hyperglycaemia in labour, not with HBA_{1C} during pregnancy [91]. Infants of women with GDM have an incidence of neonatal hypoglycaemia that approaches 30–50 % [92-94]. Cardero L et al [95] found that neonatal hypoglycaemia is found in 27% of newborn to mother with gestational diabetes mellitus and pre-existing insulin dependent diabetes mellitus.

Route of Delivery: A population based study conducted in Ontario, Canada, 1996-2001 showed that higher rates of caesarean sections in women with pregestational diabetes (PGD) than women without (PGD) [96]. A study performed by Remsberg KE, to evaluate the effect of diabetes during pregnancy on caesarian delivery .The result showed that the rate of caesarean deliveries were 23.4% [97]. Bouylvian et al conducted randomized controlled trials of elective delivery, either by induction of labor or by elective cesarean section, compared to expectant management in diabetic pregnant women at term. The results showed that the risk of cesarean section was not statistically different between groups [98]. Another study [99] found that the incidence of cesarean section was 55.9% in diabetic women. A nation wide population based study [81], to compare pregnancy outcomes in type 1diabetic women with back ground

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population. The result found that the caesarean rate is higher in diabetic women (55.9% vs. 12.6%).

Preterm Delivery: Mimouni F found that the rate of spontaneous preterm labor in diabetic women was31.1%which is significantly higher than that in control population managed by the same obstetriation in similar clinical settings (20.2%) [(100)]. Lapolla A et al [(78)], reported that the preterm delivery rate was significantly higher in type1 and type2 diabetes than non diabetic women. Another study [(99)] found the incidence of pre term delivery was 41.7%. A cohort study performed by Jacques Lep ercq etal reported that the overall rate of preterm delivery was 24% [(101)].

Pre Conception Counseling and Pregnancy Care

A study performed in 2006, to evaluate the impact of diabetes on provision counselling. The results showed that visits which made by diabetic women of reproductive age were significantly less likely to include contraceptive counselling than visits made by non-diabetic women of reproductive age [(102)]. Three studies [(103,104,105)], found the same results (Ylinen and Co-Workers [(103)], Helsinki Fuhrman, and colleagues in Germany [(104)], and Steel from Great Britain[(105)]). These studies reported dramatic decreases in the incidences of major congenital anomalies among the offspring of diabetic women who sought care preconceptionally and in whom virtual euglycemia was achieved during the early weeks of gestation. Lapolla A et al [(78)] reported that pre pregnancy counselling had been provided to 43.9% of women who had type 1 and 29.1%of women had type 2 diabetes. A study conducted by Galindo et al [(79)], showed that 11.9% of pregestational diabetic women used pre

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conception counseling.

Several studies in Arab countries concluded that pregnancy in women with diabetes has been associated with adverse effect on fetal outcomes.

A case control study was done to determine the fetal outcome in diabetic pregnant patients managed exclusively by the obstetrician at King Faisal military hospital in the southwest region of Saudi Arabia, to compare this with the non-diabetic control group in the same hospital. The sample consists of 83 diabetic and non-diabetic pregnant patients who delivered at king Faisal military hospital over a two-year period. The results showed a perinatal mortality rate in diabetic patients of 6.02% while that in the non-diabetic control group was 1.2%, and the caesarean section rate was 5 times higher in the cases than in controls [(130)].

Furthermore, in one of cross sectional survey that carried out in Ministry of Health, Kuwait, to estimate still birth rates in patients diagnosed as having NIDDM. In addition, it describes socio demographic characteristics, and diabetes related factors that distinguish women with established NIDDM who experienced repeated stillbirths from those who did not. The samples data by 99kuwaiti women with NIDDM who are still in the reproduction are from across sectional survey carried out in 1995/96. The result reported that the stillbirth rate was 76.5% in comparison to 6.9% from general population [(131)]. Beside those studies, one study in Benghazi that was done from 1st of June 1984to1st June1991, 988pregnant diabetic patients were treated by a team of physicians and obstetricians in Benghazi diabetic clinic. The majority, 64.5%delivered vaginally and 35.5%by caesarean section, rates of abortion, intra

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uterine fetal death and still birth were 7.99%, 3.28%and 2.6%respectively. Congenital anomalies of infant were 3.4% [132]. Khwaja SS [133] reported that infants born to diabetic mothers were heavier than the infants of non-diabeticmothers.

Birth Control

Effective contraception is essential for women with type 1 and type 2 diabetes to plan a pregnancy while in optimal glycemic control, reducing their offspring's risk of congenital malformations [106,107]. Similarly, women with previous GDM should use effective contraception permitting glycemic status to be assessed before any pregnancy. Oral contraception remains the most popular form of birth control despite the risk of potential side effects. The main reasons for their popularity are their low failure rate (<1%) and easy for use. Recent Cochrane review of hormonal versus non-hormonal contraceptives in women who have diabetes found three studies that met quality criteria [108]. One study compared the influence of the levonorgestrel releasing intra uterine device versus copper IUD on carbohydrate metabolism in women who have type 1 diabetes mellitus [109], no differences were found in daily insulin requirement, HBA_{1C} levels, or fasting blood sugar after 12 months of use. The other two studies were described as having limited methodology quality and compared women taking progestin only pills with women taking different estrogen /progestin combinations [110,111].The results reported that blood glucose levels remained stable during treatment with most regimens.

Several studies [112,113,114] reported that the use of low-dose combination oral

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contraceptives (OC) and progestin-only OCs (0.35 mg norethindrone) in women with type 1 diabetes appears to produce minimal metabolic effects. Retrospective, cross-sectional studies and case-control trials [115,116] in women with type 1 diabetes have not found any increased risk or progression of diabetic sequelae (retinopathy, renal disease, or hypertension) with past or current use of OCs when controlling for the known risk factors for diabetic sequelae.

In a retrospective case-control study following-up two groups of young women with type 1 diabetes for up to 7 years who had either used or never used oral contraception, there was no difference in the mean HbA_{1c} levels, the mean albumin excretion rates, or retinopathy scores. Similarly, in a cross-sectional study of 384 women[116] with type 1 diabetes, no association was found between the use of OCs, either current, past or present, and the severity of retinopathy, hypertension, or glycosylated haemoglobin when controlling for the known risk factors for diabetic sequelae [115].

In women with previous GDM, short-term studies have shown minimal effect of low-dose combination OCs on carbohydrate and lipid metabolism [117,118]. In retrospective cohort of 904 women with previous GDM, the long-term use of low-dose combination OCs was shown not to influence the development of diabetes [119], the cumulative incidence rates for diabetes were virtually identical for women with 3 years of uninterrupted use of combination OCs (25.4%) and non-hormonal forms of contraception (26.5%). In contrast, [143,144] the use of the progestin-only OC [119] (0.35 mg norethindrone) during breastfeeding increased diabetic risk almost threefold, and the risk increased with the duration of uninterrupted use. Thus, the progestin-only OC Should not be prescribed in breastfeeding women with previous GDM. Cross

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sectional study [120] was under taken to determine whether users of oral contraceptives in nationally representative population of US women had abnormal glucose metabolism. The results showed that oral contraceptive formulations currently available in the United States are not associated with an adverse glucose metabolic profile. In a large prospective observational cohort study[119]of Latino women with prior (GDM) followed for up to 7 years after pregnancy, COC use was not associated with increased risk of type 2 diabetes compared with similar women not using hormonal contraception .

A study conducted by a Catherine Kime et al found that [121] current use of OCs is associated with lower glucose levels in young African American and white women and may be associated with lower odds of diabetes.

The intrauterine device (IUD) offers an excellent and long-acting metabolically neutral contraceptive choice in diabetic women. Use of the newer, medicated, copper IUDs have not been associated with any increased risk of pelvis inflammatory disease after the post insertion period in healthy women or in women with type 1 or type 2 diabetes and thus would be the preferable choice of IUD in diabetic women. However, as the risk of pelvic inflammatory disease associated with the use of medicated IUDs is extremely rare in the general population, making it highly unlikely that large enough studies can ever be conducted in diabetic women to demonstrate no increase in risk [122,123]. No apparent contraindications exist to IUD use in women with previous GDM. Selection of proper candidates for IUD use and monitoring of IUD use in women with diabetes or previous GDM are similar to the guidelines for the general population [123]. Prospective controlled study [124] followed 59 women with type1 diabetes and 1,043 non-diabetic users of a copper IUD for 3years. In 1,754 cumulative months of use, no instances of PID occurred among the diabetic users.

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Rates of failure, expulsion, and bleeding were similar in both groups. Another study was performed in Italian [125], to determine the pattern of contraception used by diabetic women. The result showed that 30.4% used hormonal contraception, 12%intra uterine device (IUD).

Breast-Feeding

Prospective observational cohort study of 83 585 parous women in the Nurses' Health Study (NHS) and retrospective observational cohort study of 73 418 porous women in the Nurses' Health Study II (NHS II), to evaluate the association between lactation history and incidence of type 2 diabetes among parous women, it was found that increasing duration of lactation was associated with a reduced risk of type 2 diabetes [126]. Growing Up Today Study (GUTS) performed in 2006, to evaluate beneficial effect of breast-feeding on childhood obesity showed that the breast feeding was inversely associated with childhood obesity regardless of maternal diabetes status or weight status [127]. Ute M. Schaefer, found that breast-feeding for >3 months appears to be negatively associated with overweight in early childhood [128]. A case-control study examined breastfeeding and risk of type 2diabetes in the offspring in 46 children below 18 years of age with type 2 diabetes and control group age- and sex-matched control subjects from a clinic serving Native Canadians. Their mothers had pre-existing type 1 diabetes, GDM, or no diabetes during pregnancy. The risk of type 2 diabetes was lower among offspring who were breastfed longer than 12 months versus none (OR 0.24, 95% CI 0.13–0.84) adjusted for type of maternal diabetes during pregnancy [129]. The American Academy of pediatrics recommends that mother's

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breastfeed their infants for at least 1 year [140].

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Chapter Three

METHADOLOGY

Design: comparative study conducted to answer the research questions.

Setting: The study was conducted in the National Center of Diabetes, Endocrine and Genetics (NCDEG) in Amman- Jordan in the period from September 2007 to January 2008.

The center was established in Amman in 1998 as one of the centers attached to the higher council for science and technology .The center is considered the only specialized national centre for diabetes, endocrinology, and genetics in Jordan. The patients come to the center from all over the country, directly, or referred from other clinics in the kingdom.

Study population: The sample size was 1500women.They were divided into two groups: first group included consecutive cooperative married and fertile female patients with diabetes (type1 diabetes, or type 2 diabetes, or gestational diabetes) attending National Centre of Diabetes, Endocrine, and Genetics clinics. The second group included non-diabetic cooperative healthy women who are relatives of children treated in the same center, and primary health care provider.

Exclusion criteria: unmarried and nulligravidae women were excluded.

Data collection method: data collected through structured interview, participants were informed about the purpose of the study and after their consent, were

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interviewed for seven sections that included the following:

1- Socio demographic variables included marital status, and level of education.

2- Menstrual cycle history

3 -Birth control and family planning.

4- Preconception counselling for last pregnancy.

5 - Pregnancy care for last pregnancy.

6- Pregnancy outcome for last pregnancy.

7- Breast feeding history.

This information was recorded on the data sheet.

Operational definitions for the study variables are:

Reproductive health: within the frame work of WHO's definition of health as a state of complete physical, mental and social well being, and not merely the absence of disease or infirmity, reproductive health addresses the reproductive processes, functions and system at all stages of life [(134)].

Menarche: was defined as the occurrence of the first menstruation, may occur as early as age 9 or as late as17 and still be within normal limits [(49)].

Menstrual cycle: was defined as episodic uterine bleeding in response to cyclic

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hormonal changes, with duration of menstrual flow 2-7days and interval between cycles from 23-35[49].

Spontaneous abortion was defined as the loss of a pregnancy before fetal viability (22 weeks gestation) [135].

Term: - Termination of pregnancy from 37completed weeks to less than 42 completed weeks of gestation [136].

Pre term: Termination of pregnancy before 37completed weeks of gestation [136].

Caesarean delivery: Abdominal delivery of the baby by laparotomy and section of uterus [138].

Congenital malformations: - were those responsible for death, those causing a significant future disability, or those requiring major surgery for correction [77].

Hypoglycemia: defined as blood glucose levels below 40 mg/dL (2.2 mmol/L) [30].

Macrosomia: was defined as fetal weight greater than 4.0 or birth weight above the 90th percentile for gestational age [27].

Planned pregnancy was defined as a pregnancy that was desired before conception and in which contraception was stopped or avoided for the purposes of becoming pregnant and in which Woman stated that she attempted to achieve optimal blood glucose control before becoming pregnant [139].

Family Planning: implies the ability of individuals and couples to anticipate and attain their desired number of children and the spacing and timing of their births. It is achieved through use of contraceptive methods and the treatment of involuntary

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infertility [137].

Breast-feeding: Feeding a baby by allowing him/ her to suck at the mother breast [138].

Gestational hypertension: was defined as systolic blood pressure level ≥ 140mmHg or a diastolic blood pressure level ≥90 mmHg after 20 weeks of gestation on two occasions at least 6h apart in women with previously normal blood pressure[141].

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Statistical Analysis

Statistical analysis carried out using statistical package for social science (SPSS, version 12), under guidance and supervision of Dr Yousef Khader. Initially, the data were examined for data entry errors and outlying values. Detected errors were corrected as appropriate. Descriptive statistics were obtained, such as mean values for continuous variables and proportions for categorical variables, to compare reproductive heath and birth control histories, were assessed for statistical significance, using chi square test for categorical variables, and on independent t-test for continuous variables. Multi variant logistic regression was used to assess the independent effect of given variable after adjustment for other potential confounders. Separate regression models were used for spontaneous abortion, stillbirth, intra uterine fetal death, neonatal death, P value <0.05 was considered statistically significant.

Ethical Consideration: The study was approved by the National Centre of Diabetes, Endocrine and Genetics(NCDEG) ethics committee, the study depended basically on confidentiality ,as data were used only for scientific aspects, more over, participation was optional and the data were conducted after taking the verbal approval of participants.

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Chapter Four

RESULTS

1-socio demographic characteristics of study population

This study included 1500 women they were divided into two groups, 750 diabetic women (5 women in type 1, 286in type 2, and 459 in gestational diabetes mellitus) and 750non diabetic women. Majority of study population were educated, 83.5 % were diabetic women, and 91.6% were non-diabetic as shown in figure1, and table1.

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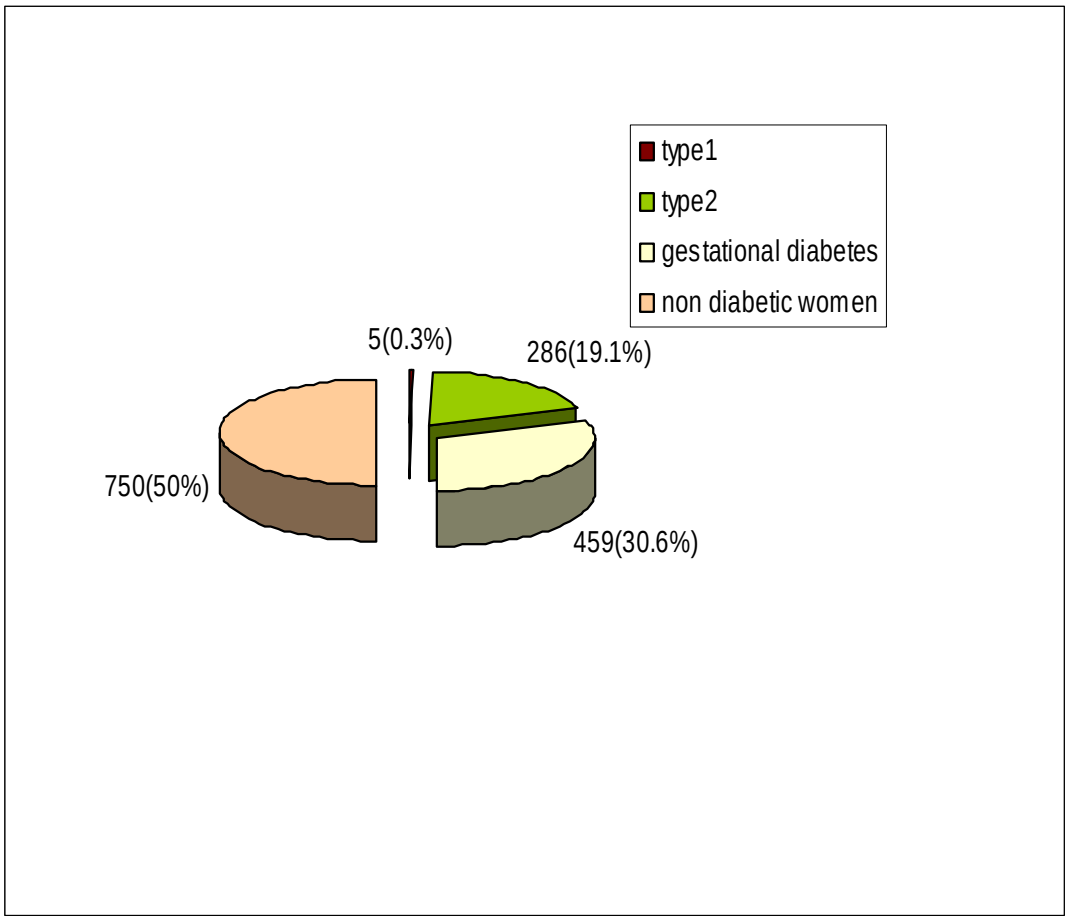

Figure1. Distributions of Study Population

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Table1.The Socio Demographic Characteristics of Study Population

Variable	Diabetic n (%)	Non diabetic n (%)
Marital status		
Married	718 (95.7)	721 (96.1)
Divorced	8 (1.1)	21 (2.8)
Widow	24 (3.2)	8 (1.1)
Level of education		
Illiterate	124 (16.5)	63 (8.4)
Educated	626 (83.5)	687 (91.6)

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Puberty (Menstrual History)

The range of age at menarche was (9-19) years in both diabetic and non-diabetic. The mean ±SD age of menarche in diabetic women was 13.4 ± 1.59 and 13.3± 1.60in non-diabetic women. There is no statistically significant difference between the mean age of menarche in diabetic women and non-diabetic women. There was no significant difference in the duration or the length of the cycle in both groups. While diabetic women reported more irregular cycles than non-diabetics as shown in table2.

Table2. Puberty (Menstrual History)

Variable	Diabetic Mean (SD)	Non diabetic Mean (SD)	P-value
Age of menarche	13.3 (1.6)	13.4 (1.5)	0.06
Duration of menstrual cycle	5.6 (1.4)	5.5 (1.3)	0.24
Duration between two menstrual cycles	28.8 (4.7)	28.6 (2.7)	0.39

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As shown in table (3), intra uterine device was the most common method of contraception used by the two groups, (43.3%, 45.9% respectively).While tubal ligation was used more in diabetics. 24.1%of diabetics and 20.7%of non-diabetics changed their method of contraception mainly due to side effects.

Table3.Birth Control and Family Planning

Variable	Diabetic n (%)	Non diabetic n (%)
Family planning method		
Intra uterine device (IUD)	325 (43.3)	344 (45.9)
Isolation	136 (18.1)	130 (17.3)
Tubal legation	69 (9.2)	33 (4.4)
Oral contraception	120 (16.0)	110 (14.7)
Condom	27 (3.6)	33 (4.4)
Progestin oral contraception	1 (.1)	
Nothing	72 (9.6)	100 (13.3)
Use more than one method for family planning		
Yes	181 (24.1)	155 (20.7)
No	569 (75.9)	595 (79.3)
Reason to change method		
Not effective and pregnancy happened.	29 (16.02)	26 (16.77)
Presence of side effect.	128 (70.71)	115 (74.19)
Fear of infertility	24 (13.25)	14 (9.03)

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Preconception counselling and planned pregnancy (for the last pregnancy)

Only 10% of diabetic women and 14.9% of non-diabetic women had planned their pregnancy. Majority of study population received counselling on first trimester. Although non-diabetic women received folic acid more than diabetic women, they are both used folic acid when they know that they are pregnant, not before.

Table4. Preconception counselling and planned pregnancy

Variable	Diabetic n (%)	Non diabetic n (%)	P-value
Planned last pregnancy Yes No	 75 (10) 675 (90.0)	 112 (14.9) 638 (85.1)	 **0.002**
Time of first counselling visit. Before pregnancy First trimester Third trimester	 49 (6.5) 700 (93.3) 1 (0.1)	 36 (4.8) 714 (95.2)	 0.209
The period between the last 2pregnancies ≤1 years >1-2 years >2-3 years >3 years	 126 (17.4) 176 (24.2) 156 (21.5) 267 (36.8)	 137 (19.3) 187 (26.3) 154 (21.7) 232 (32.7)	 0.376
Received folic acid	476 (63.5)	580 (77.3)	**<0.005**
When was received folic acid Before 3 month of pregnancy At time of diagnosing pregnancy	 9 (1.9) 467 (98.1)	 5 (0.9) 575 (99.1)	 **<0.005**

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Pregnancy Care

88.5% of diabetic women and 90.5%of non-diabetics had follow up by obstetrician. The majority of them didn't measure fasting blood sugar during first trimester. Neither diabetic nor non diabetic women had detailed fetal abnormality scan to detect congenital abnormality, and none of them had measurement of maternal serium α fetoprotein(MSAFP).

table5. Pregnancy Care

Variable	Diabetic n (%)	Non diabetic n (%)	P-value
Regular follow up during pregnancy Yes No	 496 (66.1) 254 (33.9)	 499 (66.5) 251 (33.5)	 0.456
Provider during pregnancy Diabetologest Obstetrician No body	 2 (0.3) 664 (88.5) 84 (11.2)	 679 (90.5) 71 (9.5)	 0.196
Measurement of fasting blood sugar during first trimester	223 (29.7)	143 (19.1)	**<0.005**
Measurement of fasting blood sugar during second trimester	436 (58.1)	234 (31.2)	**<0.005**
Measurement of fasting blood sugar during3rd trimester	687 (91.6)	677 (90.3)	0.209
Gestational hypertension	156(20.8)	20 (2.7)	**<0.005**

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Pregnancy Outcome: Poor pregnancy outcome indicators were significantly higher in diabetics than the non-diabetics. This include macrosomia, neonatal hypoglycemia, spontaneous abortion, pre term delivery, still birth, neonatal death, congenital abnormality, and intra uterine fetal death as shown in table 6.

Table6.Pregnancy Outcomes

Variable	Diabetic n (%)	Non diabetic n (%)	P-value
Macrosomia	245 (40.2)	30 (4.2)	**<0.005**
Neonatal hypoglycemia	155 (20.7)		
Spontaneous abortion	141 (18.8)	42 (5.6)	**<0.005**
Pre term delivery	116 (15.5)	46 (6.1)	**<0.005**
Still birth	67 (8.9)	20 (2.7)	**<0.005**
Neonatal death	53 (7.1)	11 (1.5)	**<0.005**
Congenital abnormality	37 (4.9)	8 (1.1)	**<0.005**
Intra uterine fetal death(IUFD)	26 (3.5)	13 (1.7)	**0.025**

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Diabetic mothers were significantly older than non-diabetic at their last pregnancy. The caesarean section rate was significantly high in diabetics than non-diabetics. The percentage of women who breast-feed their babies was significantly lower in diabetics compared to non-diabetics. The mean of total gravida in diabetic women was 5.8 and 4.6 in non-diabetic women (Table7).

Table7. Breast Feeding History:

Variable	Diabetic N (%)	Non diabetic N (%)	P-value
Age of mother at last pregnancy, mean(SD) <35 ≥35	34.7 (4.67) 319 (42.5) 431 (57.5)	32.9 (5.26) 447 (59.6) 303 (40.4)	**<0.005** **<0.005**
Route of delivery Vaginal delivery Caesarean delivery	 528 (70.4) 222 (29.6)	 634 (84.5) 116 (15.5)	**<0.005**
Breast feeding	352 (46.9)	478 (63.7)	**<0.005**
Duration of breast feeding, mean (SD)	4.9 (6.77)	6.9 (7.17)	**<0.005**
Total gravida, mean (SD)	5.8 (2.2)	4.6 (2.09)	**<0.005**

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Logistic regression analysis was made for a number of variables in the last pregnancy. This included spontaneous abortion, preterm delivery, stillbirth , neonatal death, macrosomia, congenital abnormality, and intrauterine fetal death. The odds ratio is shown in table8.

Spontaneous abortion

After adjusting for other variables, the odds of having spontaneous abortion in diabetic women were 3.6 times more than non-diabetic women.

Preterm delivery

After adjusting for other variables, the odds of having preterm delivery for the last pregnancy in diabetic women was1.9 time's more than non-diabetic women.

Stillbirth

After adjusting for other variables, the likelihood of stillbirth in diabetic women 3.81times than non-diabetic women.

Neonatal death

The risk of neonatal death in diabetic women 5.10 times more than non-diabetic women, after adjusting for other variables.

Congenital abnormality

The odds of having congenital abnormality in diabetic women 4.81 times more than non-diabetic women. After adjusting for other variables.

Intra uterine fetal death

After adjusting for other variables, there is no significant different between diabetic women and non-diabetic women to have intra uterine fetal death.

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Odds Ratio of the Difference between Diabetes and Non-Diabetes for each Pregnancy Outcomes, after Adjusting Demographic and Health Variables.**

Table8.

Variable	*OR (95 % CI)	P value
Spontaneous abortion	3.60 (2.50, 5.18)	**<0.005**
Preterm delivery	1.98 (1.35, 2.90)	**<0.005**
Still birth	3.81 (2.26,6.42)	**<0.005**
Neonatal death	5.10 (2.64 ,9.86)	**<0.005**
Macrosomia	14.56 (9.75 , 21.75)	**<0.005**
Congenital abnormality	4.81 (2.22 , 10.40)	**<0.005**
Intra uterine fetal death	1.02 (.47 , 2.21)	0.94

***OR (diabetics vs. non diabetics)**

****Adjusted for** (age of the mother for last pregnancy, level of education, planned last pregnancy, received folic acid, measurement of fasting blood sugar in first trimester,2nd trimester, and 3rd trimester, follow up during pregnancy).

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DISCUSSION

This study compares reproductive health history, pregnancy outcomes, birth control and family planning practices among diabetic and non-diabetic women in reproductive age group.

The effect of diabetes at the age of menarche is inconsistent in different studies. In Our study the mean age at menarche was not different in both diabetic and non diabetic women (13.3%, 13.4%, p value 0.06 respectively), this finding agrees with some studies [67, 68] and disagrees with others [16, 17, 66, 71, 70, 79] which had found a delay of age of menarche from 3month to one year according to age of developing insulin dependent diabetes.

Diabetes is the most common medical condition that complicates pregnancy. Our results showed that the outcomes of pregnancy in diabetic women remain poor compared to non-diabetic women. We found that the rate of congenital malformations in infant of diabetic women was (4.9%), and it was five times more than in non-diabetic women (1.1%),which was consistent with other studies in Italy[78](4.9%),France[75](4.1%), North East England[22] (4.0%) , and in Benghazi[132](3.4%).

In this study, we found a four-fold increase of spontaneous abortion in diabetic compared with non-diabetic women (18.8%vs. 5.6%).Which is similar to other studies [79, 80, 85].

In the current study, we found a twofold increase in stillbirth in diabetic compared

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with non-diabetic women (8.9%vs. 2.7%).This is in agreement with the Italian study [78] that reported stillbirth were 1.26 %vs. 0.3% in diabetic and non-diabetic women respectively. Also Dos Santos et al reported a rate of stillbirth of 2.5% [86]. A study conducted in Kuwait [131] showed that the rate of stillbirth in type 2diabetes was 67,5% compared to 6.9 % in the general population, and another study conducted in Benghazi found that the rate of stillbirth was2.6 %[132].

Our data showed that the prevalence of neonatal death was higher in diabetic than non-diabetic women (7.1% vs.1.5%). This finding was in agreement with the Italian study [78] in which neonatal death in diabetic and non-diabetic women were (0.63%, 0.32% respectively). Also Dos Santos et al reported a rate of neonatal death of 1.2% [86]. Neonatal death in our study was higher than Italian study. This is possibly due to better care and education in the developed countries compared to our part of the world.

In the current study, the proportion of intra uterine fetal death (IUFD) among diabetic women was 3.5% compared to non-diabetic women (1.7%), which was consistent with study done in Benghazi[132], which found the rate of IUFD in diabetic women to be 3.28 %.

Our data showed that the proportion of neonatal hypoglycaemia in infant of diabetic women was 20.7%, which is lower than that reported by other studies [92, 93, 94, 95]. These differences might be due to different methodology and sample size.

Infants of diabetic mothers in the present study had a high rate of macrosomia (40.2%) whereas in non-diabetic women the rate was (4.2%). This result was supported by results of studies from Novo Scotia [87] which showed that macrocosmic infants of diabetic mothers was 45.2%compared with 12.6%of non diabetic mothers.

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In addition, other studies [88, 89]. However, the difference in the proportion of macrosomia in many studies depends widely on the methodology, the sample size, and the cut off points for weight to be considered as macrosomia.

Many studies [78, 99,101] reported that preterm delivery rate was significantly higher in diabetic women than non-diabetics were. In our study, proportion of preterm delivery among diabetic women was (15.5%) whereas in the non diabetic women was(6.1%).This result is supported by the study conducted by Mimouni F [100] who found that the rate of preterm delivery in type 1 diabetes to be 31.1% compared to 20.2%in non-diabetic women.

In accordance with other studies [81,96,97,98,99,132] we found that caesarean section is significantly more frequent in diabetic women than in the general population, probably as a consequence of more frequent obstetric complication (preterm delivery, preeclampsia, and macrosomia). The rate of caesarean section in our study was 29.6%, which is higher than in non-diabetic women (15.5%).

In our study, there are many factors, which might affect outcomes of pregnancy in diabetic women; **first**, the age of diabetic women was higher than that of non-diabetics. **Second**, the multi parity of diabetic mother compared to non-diabetic women can adversely affect the outcomes. **Third**, 6.7% of diabetic women had attended to obstetrical department for first time before conception, while majority of them attended in the first trimester. There was a significant different between diabetic and non-diabetic mothers in planning their pregnancies (10%, vs. 14.9% respectively).

Fourth, none of the diabetic and non-diabetic women had a detailed ultrasound to detect congenital anomalies, and none of them had measurement of MSAFP. **Finally**, the rate of gestational hypertension in diabetic women was found to be higher than

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non-diabetic women (20.8%compared to 2, 7%).

Birth Control

Women with diabetes have many safe and effective contraceptive options. In current study, the most common method of family planning used in diabetic women was IUD (43.3%) which was almost identical to that of non-diabetic women (45.9%) which is contrast to Italian study [125]. This finding can be attributed to the fact that more than 50%of our diabetic population, were≥35 years and were multi parous. We have found that our diabetic women had used tubal legation as a method for contraception more than non-diabetic women, a factor which can be attributed to the multiparity of diabetic women. However, the intra uterine device is very effective, reversible contraceptive method without metabolic disturbances, and offer excellent pregnancy protection with failure rates below1 %[123,124, 140]. 24.1%of diabetic women used more than one method for planning their pregnancy for different reasons, compared with non-diabetic women 20.7 %.This finding can be explained by the fact that they have insufficient knowledge about birth control methods to reduce risk of unplanned pregnancy.

Breast-Feeding

Is recommended, as the preferred method of infant feeding for the first year of life or longer because breast-feeding was inversely associated with childhood obesity regardless of maternal diabetes status or weight [140]. In our study we have found that the mean duration of breast feeding in diabetic women was 4.9months which was lower than the mean duration of non diabetic women(6.9)months. This finding could be explained by many factors; poor knowledge of the patients regarding the misconception of transferring diabetes mellitus to her baby by lactation , in addition

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to the use of oral hypoglycaemia agents, which is a contraindication for breast-feeding.

Strength and limitation of the study

The process of selection of this study sample was not to be intended a representative sample of all diabetic women in Jordan. However, the pool of diabetic patients that report to the center from all over the country and the large sample size included in the study encourage us to believe that Jordanian diabetic women are well represented in this study.

Advantages of our study include large sample size, non-invasive method, cost effectiveness, and the lack of previous similar studies in Jordan. Our study has the limitation of recall bias especially with the grand multi parous women, and the shortage of records of blood sugar, postprandial blood sugar, HBA_{1C}, and blood pressure, so we need further study to follow diabetic women from time of planning their pregnancies to time of delivery in longitudinal study to assess the effect of diabetes on reproductive health and pregnancy outcomes.

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CONCLUSIONS

Adverse pregnancy outcomes in diabetic women remain high compared with non-diabetic women.

Diabetes was found to be independently associated with serious adverse outcomes in pregnancy compared with non-diabetic women.

Unplanned pregnancy was high in both diabetic and non-diabetic.

Our results showed that there was an insufficient knowledge about family planning method selection, and the use of appropriate method.

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RECOMMENDATIONS

More keen attention must be given for preconception counselling, and adequate maternal glucose control maintenances near physiologic level before conception and throughout pregnancy to decrease the likelihood of spontaneous abortion, still birth, neonatal death, hypoglycaemia, and macrosomia .

Proper antenatal screening and follow up are advised.

Criteria for selecting contraception should include safety, effectiveness and should be individualized for each woman's situation.

Young women should also be instructed on the importance of taking folic acid.

Early diagnosis of gestational diabetes mellitus is an important step to improve outcomes and screening for diabetes should be offered to all pregnant women.

Breast-feeding should be encouraged in women with both pregestational and gestational diabetes for at least one year.

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APPENDIX A

Data sheet:

Socio demographic Data:

- File Number: ----------

1-Marital status:

1- Married 2-Divorced 3- Widow

2-Level of education:

1- Illiterate 2 –Educated

3-Did you have diabetes?

1- Yes 2- No

4-If yes what is the type of diabetes?

1- Type1 diabetes 2- Type2 diabetes

3- Gestational diabetes

Menstrual cycle:

5 - Age of menarche :----------(years).

6- Duration of menstrual cycle: ---------- (days).

7- Duration between two menstrual cycles: ---------- (days).

Planned pregnancy:

8 - Method using now for family planning:

1-IUD

2- Isolation

3- Tubal legation

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4- Oral contraceptive

5- Condom

6- Progestin oral contraceptive

7- Nothing

9-Did you use more than one method for family planning?

1- Yes 2- No

10- If yes, reason to change the method?

1- Not effective and pregnancy happened.

2- Presence of the side effect.

3- Fear of infertility

11-The period between the last 2 pregnancies:

2-(<1years) 3- (>1-2years)

4 - (>2 to3) 5-(>3years)

Pre conception counseling for last pregnancy:

12-Was the last pregnancy a planned one?

1- Yes 2- No

13-Onset of first counseling for the last pregnancy:

1- Before pregnancy 2-First trimester

3- Second trimester 4- Third trimester.

14- Did you measure fasting blood sugar before conception?

1- Yes 2- No

15- Received folic acid:

1-yes 2-no

16-If yes, when was received it.

1- Before three month of pregnancy.

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2- At time of diagnosing pregnancy.

Pregnancy care for last pregnancy:

17 -Did you regularly follow up your pregnancy as prescribed by your doctor?

1- Yes 2- No

18- Health provider during pregnancy

1-Diabetologist 2-Obstetrician

3-G.P 4- No body

19- Did you measure fasting blood sugar during first trimester?

1- Yes 2- No

20 - Did you measure fasting blood sugar during 2nd trimester?

1- Yes 2- No

21- Did you measure fasting blood sugar during 3rd trimester?

1- Yes 2- No

22-Did you do U/S to detect congenital abnormalities during pregnancies?

1-Yes 2- No

23-Did you measure your maternal serum α fetoprotein (MSAFP)

1- Yes 2- No

24-Did you have gestational hypertension?

1- Yes 2- No

25-Age of mother---------- (Years)

Pregnancy outcomes for last pregnancy:

26-Spontaneous abortion (less than 22week):-

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1- Yes 2- No

27-Pre term delivery <37weeks

1- Yes 2- No

28-Full term (37-42weeks):

1- Yes 2- No

29- Intra uterine fetal death (IUFD)

1- Yes 2- No

30-Still birth during delivery

1- Yes 2- No

31- Neonatal death

1- Yes 2- No

32-Weight of baby---------- (kgm)

33-Any congenital anomalies

1- Yes 2- No

34-Need for admission NICU for hypoglycemia

1- Yes 2- No

35-Route of delivery

1-caesarean delivery 2-normal delivery

36-Did you breast feed your baby

1- Yes 2- No

37- If yes, duration of breast feeding---------- (month).

38- total gravida ----------.

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الصحة الانجابية وممارسات تنظيم الاسرة لدى السيدات المصابات بالسكري

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الملخص

تهدف هذه الدراسة الى مقارنة الصحة الانجابية ونتائج الحمل وكذلك تنظيم الاسرة بين مريضات السكري والنساء غير المصابات بالسكري في مرحلة الانجاب. دراسة مقارنة نفذت على عينة تتالف من 1500 امراة. 750 مريضة متزوجة ولديها سكري (النوع الاول او النوع الثاني او سكري الحمل) و750 امراة متزوجة وليس لديها سكري خلال الفترة ما بين ايلول 2007حتى كانون الثاني 2008 جمعت المعلومات من خلال مقابلة مكتوبة .

متوسط معدل اول ددورة شهرية في حياة المراة المصابة بالسكري هو 13.3.سنة اما بالنسبة المراة الغيرالمصابة بالسكري فهو13.4 اذ ليس هنالك اختلاف احصائي مميز.

-نسبة التشوهات الخلقية لدى اطفال نساءمريضات السكري اعلى من اطفال نساءالغير مصابات بالسكري(4.9%.1.1%على التوالي).
-نسبة الاطفال الذين توفو بعد الولادة و الاطفال الذين توفو لحظة الولادة وكذلك الاجنة التي توفت داخل الرحم هي(7.7.8.9.3.5%على التوالي)لمريضات السكري وهي اعلى بكثير من النساءالغير مصابات بالسكري (1.5.2.7.1.5 % على التوالي).وكذلك الامر بالنسبة للاطفال الذين يولدون بحجم كبير فهي اعلى نسبة لمريضات السكري مقارنة باطفال السيدات الغير مصابات بالسكري(40.2.4.2% على التوالي).

- نسبة هبوط السكر لهؤلاء الاطفال حديثي الولادة لمريضات السكري هو 2.7%.

- نسبة الولادة المبكرة لدى مريضات السكري هي(15.5%)اي اعلى بنسبة 1.9مرة من النساءالغير مصابات بالسكري(6.1).

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- نسبة اجراء عملية قيصرية لمريضات السكري هي اعلى بكثير مقارنة من النساءالغير مصابات بالسكري(29.6,5.5% على التوالي).

-اكثر طريقة شائعة الاستخدام لدى النساء في مجتمع الدراسة هو استخدام اللولب ،بينما ربط المواسير يلاحظ استخدامه اكثر لمريضات السكري.

نسبة الرضاعة الطبيعية لدى مريضات السكري هي اقل بكثير من نسبة الرضاعة الطبيعية النساءالغير مصابات بالسكري.

نتائج الحمل السلبية وجدت اكثر لدى لمريضات السكري مقارنة النساءالغير مصابات بالسكري.

- السكريعامل مستقل في احداث نتائج الحمل السلبية لدى مريضات السكري مقارنة من النساءالغير مصابات بالسكري.
- اللولب اكثر استعمالا لدى المجموعتين .
- يجب التركيز على زيادة وعي مريضات السكري حول المشورة الطبية قبل حدوث الحمل والتخطيط للحمل وكذلك استخدام وسائل تنظيم الاسرة والرضاعة الطبيعية.

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