ORIGINAL RESEARCH PAPER

Medicine

KEY WORDS:

INCIDENCE OF GESTATIONAL DIABETES IN WOMEN WHO UNDERGO INFERTILITY TREATMENT AND TO COMPARE IT WITH WOMEN WHO CONCEIVED SPONTANEOUSLY

Dr. Reshma A. M.

Dr. J. S. Divya Louis

INTRODUCTION AND BACKGROUND

In 1952, Jorgen Pederson postulated that maternal hyperglycemia led to fetal hyperglycemia, which evoked an exaggerated fetal response to insulin.

Gestational diabetes mellitus (GDM) is one of the most frequent maternal complications during pregnancy. [1] It is a condition where a woman without prior diagnosed diabetes experiences high blood glucose levels during pregnancy. It occurs when a woman's pancreatic function is not sufficient to cope with the relative insulin resistance created by the anti-insulin hormones, such as human placental lactogen, and the increased fuel consumption necessary to provide for the growing fetus. [2]

It was estimated that GDM complicates 3–5% of pregnancies worldwide. Pregnancy complicated with GDM is associated with adverse acute and long-term consequences for both mother and infant. [1]

Research has shown that pregnant women with GDM have significantly higher rates of pre-eclampsia and Caesarean section than similar pregnant women without GDM. [2,3]

Infants born to mothers with GDM are at increased risk of large for gestational age (birth weight above 90% percentile for gestational age), high cord-blood serum C-peptide levels and perinatal mortality. [2,4]

Furthermore, a long-term follow-up study demonstrates that most women with GDM will progress to type 2 diabetes. [2] Children born to women with GDM have increased risk for obesity and type 2 diabetes later in life. [2,5]

Factors which increase the risk of GDM include advanced maternal age, high pre-pregnancy BMI, family history of diabetes, pre-existing hypertension, smoking during pregnancy, parity, multiple gestational pregnancy and assisted reproduction technology treatment. [6,7,8,9,10,11]

Infertility (defined as more than 12 months attempting to achieve a pregnancy without conception) affects approximately 12–30% of couples based on estimates from prospective preconception cohorts. [12, 13, 14, 15] The underlying reasons for infertility are diverse. Common female factors include ovulatory disorders, tubal blockage, and endometriosis. Underlying obesity-related metabolic disturbances, such as inflammation and insulin resistance, have been implicated in several of these conditions, suggesting a possible shared etiology. [16,17,18,19,20]

Ovulation induction (OI) refers to a procedure that increases the production and or release of fully matured eggs from the uterus. OI is used among individuals who struggle to ovulate normally, resulting in complications becoming pregnant. Intrauterine insemination (IUI) is a type of artificial insemination where sperm is injected sperm directly into a woman's uterus, increasing the chance of live sperm coming into contact with a live egg. Fertilization by mixing sperm with eggs surgically removed from an ovary followed by uterine implantation of one or more of the resulting *fertilized* eggs.

Assisted reproductive technology (ART) is the technology used to achieve pregnancy in procedures such as fertility medication, in vitro fertilization and surrogacy. ART includes all fertility treatments in which both eggs and embryos are handled.

More and more infertile patients have accepted the assisted reproductive therapy. Concerns have been raised over an increased risk of adverse maternal outcomes in ART populations as compared with natural conception.

Advanced maternal age is the most significant contributor to GDM. Bener *et al* [9] reported that 45% of pregnant women aged 35 –45 years had GDM. Multiple gestational pregnancy is another important factor associated with GDM.

Given the higher proportion of women undergoing ART treatment, some studies suggested that ART is associated with an increased risk of GDM. [1, 10] Jones *et al* [10] suggested that women with multiple pregnancies who conceived following ART have impaired glucose tolerance compared with those who conceived spontaneously. However, Shevell *et al* [22] reported no differences in GDM between spontaneously conceived pregnancies and those who conceived through ART treatment. Also, it is not clear whether singleton pregnancies following ART treatment are also at increased risk of GDM compared with non-ART singleton pregnancies. This study, using the data of women who gave birth at Kerala Institute of Medical Sciences, Kerala during 2016–2018, aims to determine the association between ART treatment and the prevalence of GDM in singleton pregnancies.

RESEARCH QUESTION

Is there an increased risk of developing gestational diabetes in pregnancies following infertility treatment?

AIM AND OBJECTIVES

AIM:

To assess the incidence of gestational diabetes in antenatal patients who conceived following infertility treatment and to compare it with women who conceived spontaneously.

Primary Objective:

To determine the incidence of gestational diabetes in women who undergo infertility treatment and to compare it with spontaneously conceived singleton pregnancies.

Secondary Objective:

To determine the prevalence of gestational diabetes in the population.

REVIEW OF LITERATURE

Definition Of GDM

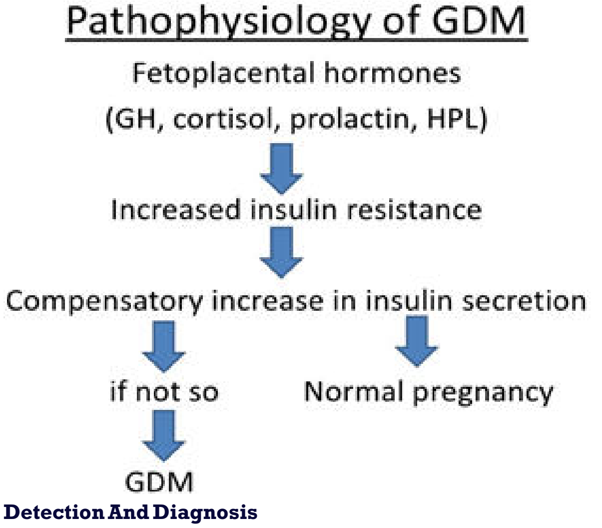
Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy. The definition applies whether insulin or only diet modification is used for treatment and whether or not the condition persists after pregnancy. It does not exclude the possibility that unrecognized glucose intolerance may have antedated or begun concomitantly with the pregnancy.

Mechanism Of Glucose Regulation During Normal Pregnancy

Fasting blood glucose decreases at early pregnancy and continuously during gestation (15) . Insulin sensitivity declines with advancing gestation to reach 50–60% of pre-gravid state at late gestation (34–36 weeks) (16). As a reflection of insulin resistance, fasting insulin concentrations increase. The changes in insulin sensitivity are inversely related to changes in maternal body fat mass (17) . The increase in hepatic glucose production during pregnancy suggest that the defect in insulin action also targets the liver. Catalano et al (18,19) found a significant increase in basal endogenous glucose production at the end of gestation in spite of the increase in fasting insulin concentration.

Alterations in maternal physiology during pregnancy are mediated by placental factors (20). Alterations in maternal metabolism are attributed to placental hormones, such as human placental lactogen (hPL), progesterone and estrogen (21,22) . The lipolytic effect of hPL allows the re orientation of maternal metabolism toward lipid rather than glucose utilization, favoring glucose sparing for the fetus. The consequent increase in free fatty acid levels may help insulin sensitivity changes in pregnancy as is the case in non-pregnant subjects (24). Kirwan et al. reported that the level of placental tumor necrosis factor alpha (TNF a) is the most important determinant of insulin resistance during pregnancy independently from fat mass changes (26).

Meanwhile insulin secretion increases as a consequence of insulin resistance. Catalano et al. (27) reported that first and second phase insulin secretion increase by almost 300% throughout gestation. This insulin secretion adaptation is probably due to the rise of maternal hormones which coincides with the development of maternal insulin resistance. In conclusion, the robust plasticity of b-cell function in the face of progressive insulin resistance is the hallmark of normal glucose regulation during pregnancy. Diabetes may occur if pancreatic b-cells are unable to keep up with heightened insulin demand during pregnancy.



Detection And Diagnosis

Risk assessment for GDM should be undertaken at the first prenatal visit. Women with clinical characteristics consistent with a high risk of GDM (marked obesity, personal history of GDM, glycosuria, or a strong family history of diabetes) should undergo glucose testing as soon as feasible. If they are found not to have GDM at that initial screening, they should be retested between 24 and 28 weeks of gestation. Women of average risk should have testing undertaken at 24–28 weeks of gestation.

A fasting plasma glucose level >126 mg/dl (7.0 mmol/l) or a casual plasma glucose >200 mg/dl (11.1 mmol/l) meets the threshold for the diagnosis of diabetes, if confirmed on a subsequent day, and precludes the need for any glucose challenge. In the absence of this degree of hyperglycemia, evaluation for GDM in women with average or high-risk characteristics should follow one of the two approaches:

One-step Approach:

Perform a diagnostic oral glucose tolerance test (OGTT) without prior plasma or serum glucose screening. The one-step approach may be cost-effective in high-risk patients.

Two-step Approach:

Perform an initial screening by measuring the plasma or serum glucose concentration 1 h after a 50-g oral glucose load (glucose challenge test [GCT]) and perform a diagnostic OGTT on that subset of women exceeding the glucose threshold value on the GCT. When the two-step approach is employed, a glucose threshold value >140 mg/dl (7.8 mmol/l) identifies approximately 80% of women with GDM, and the yield is further increased to 90% by using a cutoff of >130 mg/dl (7.2 mmol/l).

With either approach, the diagnosis of GDM is based on an OGTT. Diagnostic criteria for the 100-g OGTT are derived from the original work of O'Sullivan and Mahan, modified by Carpenter and Coustan, and is shown in Table 1. Alternatively, the diagnosis can be made using a 75-g glucose load and the glucose threshold values listed for fasting, 1 hour, and 2 hour. However, this test is not as well validated for detection of at-risk infants or mothers as the 100-g OGTT.

Table 1 Diagnostic Criteria Of OGTT

Time of testing	100g 3 h OGTT (mg/dl)	75g 2 h OGTT (mg/dl)
Fasting	95	92
1-hour	180	180
2-hour	155	153
3-hour	140	-

Two or more of the venous plasma concentrations must be met or exceeded for a positive diagnosis. The test should be done in the morning after an overnight fast of between 8 and 14 h and after at least 3 days of unrestricted diet (≥150 g carbohydrate per day) and unlimited physical activity. The subject should remain seated and should not smoke throughout the test.

Table 2: Criteria For The Diagnosis Of Diabetes Mellitus

Normoglycemia	IFG and IGT	Diabetes mellitus*
FPG <110 mg/dl	FPG ≥110 mg/dl and <126 mg/dl (IFG)	FPG ≥126 mg/dl
2-h PG † <140 mg/dl	2-h PG † ≥140 mg/dl and <200 mg/dl (IGT)	2-h PG† ≥200 mg/dl
—	—	Symptoms of DM and casual plasma glucose concentration ≥200 mg/dl

DM- diabetes mellitus; FPG-fasting plasma glucose; 2-h PG-2-h post load75gm glucose.

* A diagnosis of diabetes must be confirmed on a subsequent day by any one of the three methods included in the chart. In clinical settings, the FPG test is greatly preferred because of ease of administration, convenience, acceptability to patients, and lower cost. Fasting is defined as no calorie intake for at least 8 h.[23]

Seshiah *et al* [24], recommended DIPSI as a single step procedure irrespective of the last meal. Pregnant women attending the antenatal OPD were given 75g anhydrous glucose in 250-300ml of water and plasma glucose was estimated after 2 hours. A 2-hours plasma glucose ≥ 140 mg/dl is taken as GDM. [13] However, the cut off has not been put to test to find the correlation with adverse prenatal outcome. A value of ≥ 200 mg/dl as DM and ≥ 120 mg/dl as decreased gestational glucose tolerance has been suggested.

In 2012 Wings (Women in India with GDM Strategy) [25] started by International Diabetes Federation (IDF) to develop a model care for GDM and to find a cost-effective way of screening for GDM. The outcome of the study was that non fasting DIPSI OGTT criteria, even though high in specificity, had a very low sensitivity when compared to WHO (1999) criteria and International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria. Hence it is not suitable for a diagnostic test. Fasting plasma glucose estimation can be done in the pregnant women at early gestation, if it is normal i.e. 92mg/dl repeat single step OGTT at 24-28weeks with 75 g glucose in fasting state and apply IADPSG criteria to diagnose GDM. If fasting is 92-125mg/dl it is diagnosed as GDM and if it is ≥ 126mg/dl it is designated as overt Diabetes. To obtain International standardization they recommended to do a one-step fasting OGTT using 75g glucose and apply IADPSG criteria which if not possible, the 2 step as an alternative procedure.

In a retrospective cohort study, 656 multiple pregnancies were screened for GDM with 75g, 2-h oral glucose tolerance test at 24-28 weeks of gestation to investigate the proportion of multiple pregnancies with gestational diabetes mellitus (GDM) diagnosed using the IADPSG criteria and to identify the impact of age, body mass index (BMI), and mode of conception on incidence of GDM. When patients who conceived through heterologous assisted reproduction technology were compared with those who conceived spontaneously, there was a significant difference for GDM (31.1 vs. 13.6%, $p < 0.001$, OR 2.86). A similar finding was also observed comparing egg donation IVF/ICSI patients with homologous IVF/ICSI patients (31.1 vs. 14.8%, $p = 0.006$, OR 2.59). Incidence of GDM was significantly higher in obese than in non-obese patients (42.5 vs. 14.8%, $p < 0.001$, OR 4.88) and in women over 35 compared to younger patients (18.4 vs. 11.1%, $p = 0.01$, OR 1.81). [26]

In a nationwide population based cohort study by Holst *et al* [27], to determine whether women with a history of fertility problems have a higher risk of gestational diabetes mellitus (GDM) than women without a history of fertility problems, all live and stillbirths during 2004-2010 among women with fertility problems (n = 49,616) and women without fertility problems (n = 323,061) were identified. In total, 7,433 (2%) pregnant women received a diagnosis of GDM. Multivariate analysis showed that pregnant women with a history of fertility problems had a statistically significantly higher risk of GDM than pregnant women without fertility problems. In stratified analyses, the association between fertility problems and risk of GDM attenuated with increasing age and was more pronounced among primiparous women and women with polycystic ovary syndrome.

In a prospective population-based cohort study by Jie Zhang et *al*[28], 3216 pregnant women with gestational age ≤12 weeks, regular antenatal examination, and ultrasound identification of intrauterine pregnancy were enrolled from January 2010 to June 2013. According to their ART history, the participants were divided into two groups: ART group (contains fresh embryo transfer group or frozen-thawed embryo transfer group) and NC (natural conception) group. When compared to NC group, significantly increased rates of GDM ($p<0.01$), preeclampsia ($p<0.01$) and intrahepatic cholestasis of pregnancy (p 0.01) were observed in ART group.

In a retrospective cohort study by Xiao Q *et al* [29] including 2389 pregnant women, the medical records of 352 women diagnosed with PCOS were evaluated. Outcomes included GDM, preterm birth, low birth weight, macrosomia, and being small and large for gestational age. Women previously diagnosed with PCOS had a higher risk of GDM (adjusted odds ratio [OR] 1.55, 95% confidence interval [CI]: 1.14–2.09).

In the study by Szymanska *et al* [30] the weight gain until the diagnosis of GDM in both non-IVF and IVF groups of women was not significantly different (9.81±4.37 vs. 10.0±4.8 kg, p=0.8 respectively) with similar time at which they came under the specialist GDM care (29±4.0 vs. 28±4.5 weeks, p=0.42,). When analyzing first trimester fasting glucose levels it was found to be significantly higher in IVF group (89±16.2 vs. 83±11.3 mg/dl, p=0.04). Second trimester oral glucose tolerance test results and glucose levels during GDM treatment did not differ between the groups. No changes were noted in investigated fetal and neonatal variances: 3rd trimester Abdominal circumference, its percentile and neonatal birth weight (3 460±641 vs 3 200±440 g, p=0.22). They also suggested that PCOS cannot be an explanation for GDM in patients after IVF. Moreover, two groups, IVF and non-IVF were weight-matched, and they excluded the impact of BMI on the results.

Ashrafi M *et al* [31] studied the risks of gestational diabetes in patients undergoing Assisted Reproductive Techniques where they compared medical records of 215 women who conceived spontaneously and 145 women who conceived following ART and found that the risk of GDM is two-fold higher in women with singleton pregnancies conceived following ART compared with women who conceived spontaneously. The incidence of GDM was significantly higher in the IVF/ICSI and IUI groups (43% and 26%, respectively) compared with the spontaneous pregnancy group (10%). Their analysis demonstrated four strong risk factors for GDM: age, BMI, mode of ART and progesterone use during pregnancy.

In a population retrospective study by Wang, Nikravan *et al* [32], which included 13,732 ART mothers and 3,86,660 non-ART mothers, the prevalence of GDM was compared between ART and non-ART mothers. A larger proportion of ART mothers were aged ≥40 years compared with non-ART counterpart (11.7 versus 3.4%, $P < 0.01$). The prevalence of GDM was 7.6% for ART mothers and 5.0% for non-ART mothers ($P < 0.01$). Mothers who had twins had higher prevalence of GDM than those who gave births to singletons (8.8 versus 7.5%, $P = 0.06$ for ART mothers; and 7.3 versus 5.0%, $P < 0.01$ for non-ART mothers). Overall, ART mothers had a 28% increased likelihood of GDM compared with non-ART mothers (AOR 1.28, 95% CI 1.20–1.37). Of mothers who had singletons, ART mothers had higher odds of GDM than non-ART mothers (AOR 1.26, 95% CI 1.18–1.36). There was no significant difference in the likelihood of GDM among mothers who had twins between ART and non-ART (AOR 1.18, 95% CI 0.94–1.48). For mothers aged <40 years, the younger the maternal age, the higher the odds of GDM for ART singleton mothers compared with non-ART singleton mothers.

In a national survey which analyzed results of the first wave of the Taiwan Birth Cohort study; through stratified systematic sampling, 24,200 mother-and-child sampling pairs were obtained from a total of 206,741 live births in Taiwan in 2005; 366 of the babies were born with the use of ART. According to this study during pregnancy, ART group mothers suffered from a higher risk of pregnancy-related complications compared to the natural conception group counterparts, including gestational diabetes mellitus (6.3% Vs. 2.2%), pregnancy induced hypertension (4.1% Vs. 2%), and placenta previa (5.5% Vs. 1.7%). Fifty-one point nine percent (51.9%) of the ART group mothers were admitted during the pregnancy, which was significantly higher than their natural conception group counterparts ($p<0.001$). Additionally, babies born through ART had poorer outcomes than the natural conception groups: the low birth weight (<2500g) was

33.1% compared to 6.4% for babies born naturally.[33]

In an evidence check rapid review by the Sax Institute for NSW Kids and Families by Christos A Venetis, Georgina M Chambers. Two systematic reviews and Meta analyses show that in both twin (relative risk 1.78) and singleton (relative risk 1.53) ART pregnancies the risk of GDM is higher compared to spontaneously conceived pregnancies. A large population based cohort study from Australia identified that younger the maternal age, the higher the probability of GDM in ART pregnancies compared to spontaneously conceived ones.[34]

In a study conducted by J Koudstaal *et al* [35] which evaluated the obstetric outcome in singleton pregnancies after IVF a high rate of preterm deliveries and an increased rate of small-for-gestational age (SGA) children in comparison to the general parturient population have been reported. In this study 307 IVF pregnancies were compared with 307 control pregnancies after elaborate matching for an extensive number of maternal characteristics, as well as for the hospital that provided the obstetric care. In cases with spontaneous onset of labor, gestational age at delivery was 3 days shorter in the IVF group (275 versus 278 days, $P = 0.05$). The proportion of SGA was higher in the IVF group (16.2 versus 7.9%, $P < 0.001$). The combination of these two results denotes a distinct difference between IVF and control pregnancies.

In a meta-analysis done by Sunita Tandulwadkar *et al* [36] on obstetric outcome in women treated with IVF and PCOS, they concluded that PCOS is often accompanied by infertility that necessitates ovulation induction, using clomiphene citrate, gonadotropins or even IVF. These treatment methods are known to increase the incidence of multiple pregnancies as well as some negative consequences, including a rise in the risk for GDM, pre-eclampsia, etc. Furthermore, pregnancies established after IVF carry an increased risk for maternal complications.

The HAPO study [4] conducted on 23,316 participants calculated adverse pregnancy outcomes associated with an increase in fasting, 1 hour, 2 hour postprandial plasma glucose levels found that there is a strong and continuous association of maternal glucose levels below those diagnostic of diabetes with increased birth weight and increased serum C-peptide levels. They also found positive associations between increasing plasma glucose levels and each of the five secondary outcomes examined: premature delivery, shoulder dystocia or birth injury, intensive neonatal care, hyperbilirubinemia, and preeclampsia.

Long-term Considerations

Women with GDM are at increased risk for the development of diabetes, usually type 2, after pregnancy. Obesity and other factors that promote insulin resistance appear to enhance the risk of type 2 diabetes after GDM, while markers of islet cell-directed autoimmunity are associated with an increase in the risk of type 1 diabetes. Also women who have had GDM manifest components of the metabolic syndrome more often than do women without GDM.[37]

A history of GDM is also associated with an increased frequency of cardiovascular risk factors and cardiovascular events.[38] Offspring of women with GDM are at increased risk of obesity, glucose intolerance, and diabetes in late adolescence and young adulthood.[39]

The National Institute of Child Health and Human Development held a workshop on September 2005[40] to summarize the risks for adverse pregnancy outcomes after assisted reproductive technology (ART), develop an approach to counseling couples regarding these risks, and establish a research agenda. Assisted reproductive technology singleton pregnancies demonstrate increased rates of perinatal complications-small for gestational age infants, preterm delivery, and perinatal mortality-as well as maternal complications, such as preeclampsia, gestational diabetes, placenta previa, placental abruption, and cesarean delivery. Although it is not possible to separate ART-related risks from those secondary to the underlying reproductive pathology, the overall increased frequency of obstetric complications, including preterm birth and small for gestational age neonates, should be discussed with the couple. Significant gaps in knowledge were identified, and the basic science and clinical and epidemiologic research required to address these gaps is outlined.

MATERIAL AND METHODS

Study Area:

The study was conducted in the Department of Obstetrics, Gynecology and Infertility at Kerala Institute of Medical Sciences, Trivandrum.

Study Population:

The study included patients who underwent antenatal checkups in the Department of Obstetrics with a singleton pregnancy, conceived either spontaneously or following infertility treatment. The patients were registered at their booking visit, listed out on the basis of inclusion and exclusion criteria.

Inclusion Criteria:

- Women with singleton pregnancy
- Women with spontaneous conception and infertility treated conception
- Women with maternal age between 18-40 years
- Women who gave consent for the study

Exclusion Criteria:

- Women with multifetal pregnancy
- Women with maternal age <18 years, > 40 years
- Women with pre pregnancy diabetes
- Patients on metformin for PCOS
- Patients who denied consent for the study

Study Design: Prospective observational study.

Sample Size Estimation

Required sample size (n),

$$n = \frac{\left[z_{1-\alpha/2}\sqrt{\{2p(1-p)\}} + z_{1-\beta}\sqrt{\{p_1(1-p_1) + p_2(1-p_2)\}}\right]^2}{(p_1 - p_2)^2}$$

Desired confidence level ($Z_{1-\alpha/2}$) = 1.96

Power of the study $(1-\beta) = 80\%$

$p_1 = 10\%$ [31]

$p_2 = 4\%$

$$p = \frac{p_1 + p2}{2}$$

Accordingly, n = 46.

In the study we have included 56 women who conceived spontaneously (group 1) and 48 women who conceived with infertility treatment (group 2). A total of 104 were enrolled.

Study Duration

Two years from June 2016 to May 2018.

METHODOLOGY

Primary Outcome:

The patients selected as per the inclusion criteria were grouped based on the mode of conception –

Group 1 - spontaneous conception

Group 2 – infertility treated conception

In the first trimester, pregnant women were screened to rule out overt diabetes. Women with fasting plasma glucose ≥126mg/dl or HbA1c of over 6.5% were diagnosed with overt diabetes mellitus. Women who had fasting plasma glucose between 92-125mg/dl were considered to be GDM. Those who were normal were asked to come for an OGTT at 24-28 weeks.

At 24- 28 weeks, women were screened for GDM using a single step or two step approach as advised by the consultant considering the risk factors.50g OGCT, 75g 2 hour OGTT or 100g 3 hour OGTT was done. Thresholds were taken as in Table 1. Overt DM was diagnosed in women with FBG ≥126mg/dl. If all the values were within normal limits, OGTT was repeated at 32-34 weeks or a fasting, 1 hour postprandial serum glucose values at the later gestations. Follow up was done in all cases throughout the course of pregnancy.

OGCT values more than 130 were taken as cut-off for OGCT in two step procedures. For OGTT fasting values >/=92mg/dl, 1 hour value >180mg/dl, 2 hour values > 153mg/dl, 3 hour value > 140mg/dl were considered abnormal. Any two abnormal values were considered diagnostic of GDM.

Secondary Outcome:
The prevalence of GDM in the study population was studied.

DATA COLLECTION METHODS:
The data were collected from the subjects through a data collection form and the results of lab tests and other relevant details were collected from their electronic medical records; the consent for which was obtained at the time of entry to the study.

Statistical Methods
All data were entered into MS Excel and analyzed using the statistical software SPSS version 16. Descriptive statistics were summarized using means and proportions. The incidence of gestational diabetes was compared between spontaneous conception and infertility treated groups. Chi-square test was used for comparison of categorical variables. A p-value of < 0.05 was considered statistically significant.

Ethical Consideration
Approval from Institutional Human Ethics Committee was obtained, and informed consent was collected before the study.

RESULTS AND OBSERVATIONS
The study was conducted on 104 women who were selected based on the inclusion, exclusion criteria.

Socio Demographics
1. AGE
Mean age (± SD) = 28.90 ± 4.30 years of age

Percentage Distribution Of The Sample According To Age

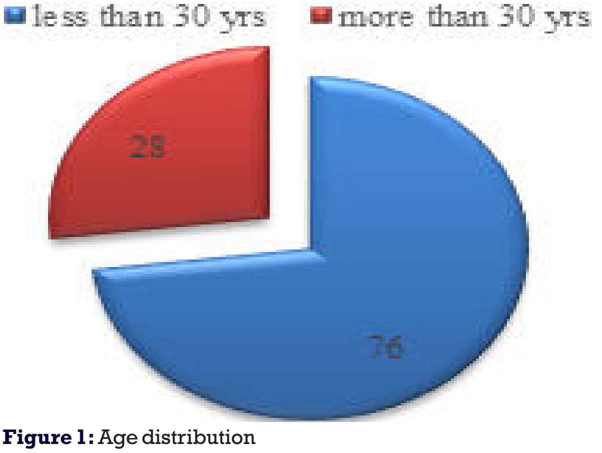


Figure 1: Age distribution

Table 3: Distribution Of Sample On Age Basis

Age group	Count	Percentage
Up to30 years	76	72.4
>30 years	28	27.6
Total	104	100

In the study population, the number of women within the age group of up to 30 years was 72.4 % (n=76) which formed the majority, while only 27.6 % came under the group of age above 30 years.

PARITY
Table 4: Percentage Distribution Of The Sample According To Parity

Obstetric score	Count	Percentage
Primipara	61	57.6
Multipara	43	42.4
Total	104	100

In our study population, 57.6 % (n=61) were primiparas whereas 42.4 % (n=43) were multiparas.

RELEVANT HISTORY
1. Past History Of Gestational Diabetes
Table 5. Distribution Of Sample Based On Past History Of GDM

Past history	Count	Percentage
Absent	100	96.1
Present	4	3.9
Total	104	100

In our study sample, 100 women were without any previous history of gestational diabetes, which contributed to 96.1 %. Only 4 (3.9 %) had history of gestational diabetes in previous pregnancies.

2. Family History
Table 6. Distribution According To Family History Of GDM, DM

Family history	Count	Percentage
Absent	55	52.8
Present	49	47.2
Total	104	100

Among the study population, 52.8 % (n=55), had no family history of GDM/ DM. But, 47.2 % (n=49) had history of GDM, DM in family.

3. Obstetric History
Table 7. Distribution Of Sample Based On Mode Of Conception

Mode of conception	Count	Percentage
Spontaneous (group 1)	56	53.8
Infertility treated (group 2)	48	46.2
Total	104	100

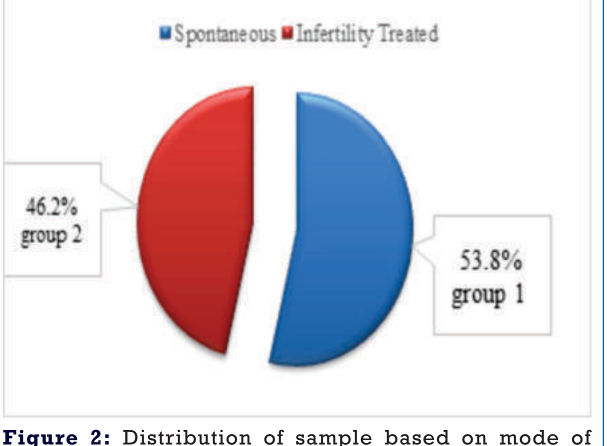


Figure 2: Distribution of sample based on mode of conception.

In our study population, 56 woman conceived naturally, which contributed to 53.8%; who constituted to the group 1; while 48 (46.2%) conceived by infertility treatment, who formed the group 2.

Table 8. Type Of Infertility

Type of infertility	Count	Percentage
Primary	36	75
Secondary	12	25
Total	48	100

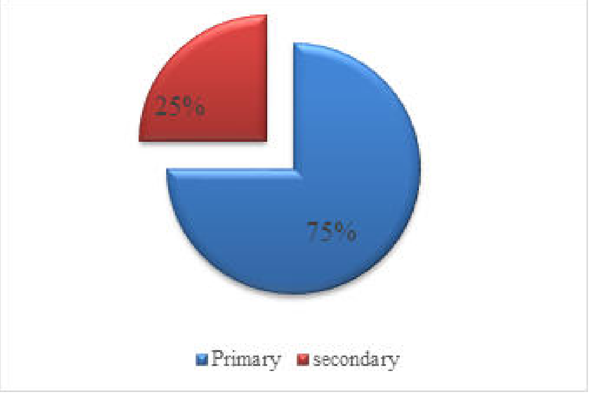


Figure 3: Type of infertility

Among the study population a total of 48 women gave history of some type of infertility treatment. 75% (n=36) of women had history of primary infertility. Only 25 %(n=12) had history of secondary infertility.

Table 9. Type Of Treatment Taken For Infertility

Type of treatment	Count	Percentage
OI	9	18.7
IUI	16	33.3
IVF	23	48
Total	48	100

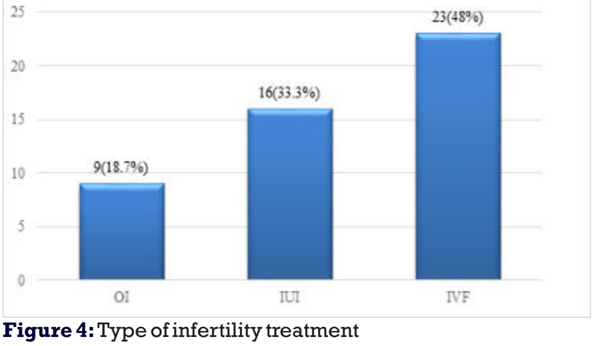


Figure 4: Type of infertility treatment

Among the 48 women who received infertility treatment, 18.7 % (n=9) had ovulation induction (OI), 33.3% (n=16) had IUI; whereas 48% (n=23) underwent IVF.

Table 10. Pre-pregnancy BMI

Pre-pregnancy BMI	Count	Percentage
<20 kg/m^2	10	9.6
20-25 kg/m^2	52	50
>25 kg/m^2	42	40.4
Total	104	100

Among the study population, 9.6 % had pre-pregnancy BMI less than 20 kg/m^2, 50% had BMI between 20-25 kg/m^{2}and 40.4% had BMI more than 25%. The second category of pre-pregnancy BMI between 20-25 kg/m^{2}constituted the majority.

Table 11. Distribution Based On Weight Gain In Pregnancy

Weight gain	Count	Percentage
Less than 5 kg	10	9.6
5-10kg	39	37.5
More than 10kg	55	52.9
Total	104	100

In the study population, in the study population 9.6% had weight gain in pregnancy less than 10kg. 37.5% had weight gain between 5-10kg, whereas the majority 52.9% had a weight gain more than 10kg.

Table 12. Use Of Hormonal Supports

Hormonal support	Count	Percentage
No	47	45.2
Yes	57	54.8
Total	104	100

Among 104 women, 47 had no history of hormonal supports used anytime in pregnancy, whereas 57 gave history of some method of hormonal supports used during the course of pregnancy.

Incidence Of Gestational Diabetes

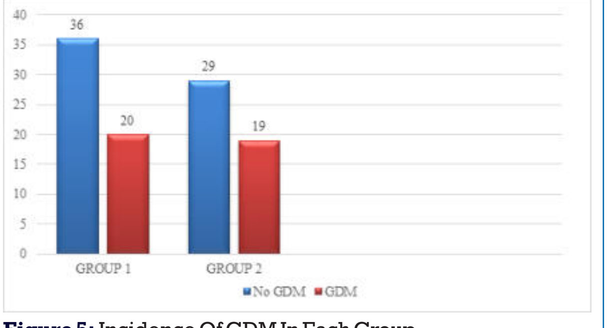


Figure 5: Incidence Of GDM In Each Group

Table 13: Occurrence Of Gestational Diabetes

GDM	COUNT	PERCENTAGE
NO GDM	65	62.5
GDM	39	37.5
TOTAL	104	100

Among the study population 62.5% (n=65) had not developed GDM, whereas 37.5% (n=39%) developed GDM.

Table 14: Comparison Of Incidence Of GDM Between Two Groups

GDM	GROUP 1	GROUP 2
Absent	36 (64.2%)	29 (60.5%)
Present	20 (35.8%)	19 (39.5%)
Total	56 (100%)	48 (100%)

Among the study population, 64.2% (n=36) of the group 1 subjects did not develop GDM, whereas 35.8% developed GDM. Considering the incidence in group 2, 60.5% (n=29) did not develop GDM, whereas 39.5% (n=19) developed GDM.

Table 15: Difference In Incidence Of GDM Among Group 1 And Group 2.

Mode Of Conception	GDM	
	Absent N=65	Present N=39
GROUP 1	36(64.3%)	20(35.7%)
GROUP 2	29(60.4%)	19(39.6%)

p value=0.69*

*p value <0.05 -significant

Among the study population, in group 1 - 35.7% (n= 36) developed GDM, whereas in group 2 – 39.6% developed

GDM. There is no statistically significant difference in the incidence of GDM among spontaneous and infertility treated pregnancies.

Table 16: Association Between Age Group And GDM

Age Group	GDM	
	Absent(N=65)	**Present N=(39)**
Less than 30yrs	52(68.4%)	24(31.6%)
More than 30yrs	13(46.4%)	15(53.6%)

p value = 0.04*

*p value <0.05 –significant

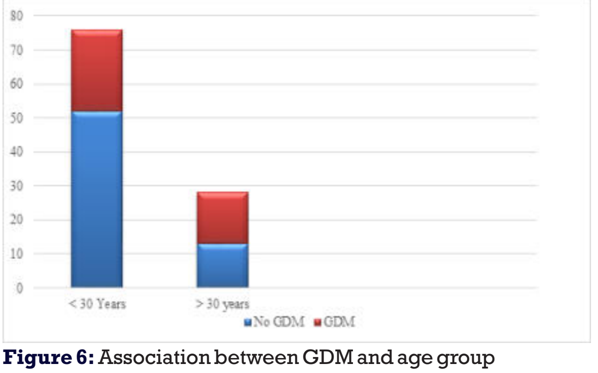


Figure 6: Association between GDM and age group

Among the study participants those who had age more than 30years,53.6% develop GDM compared to age group less than 30 years. (31.6%). There is a significant difference in the incidence of GDM between these two age groups (p value 0.04).

Among the >30years age group, 32.1% (n=9) conceived spontaneously, whereas 67.9% (n=19) had infertility treatment. In the infertility treated group, 52.6% (n=10) developed GDM.

Table 17: Prevalence Of GDM In Study Population

GDM	COUNT	PERCENTAGE
NO GDM	65	62.5
GDM	39	37.5
TOTAL	104	100

Among the study population of 104, 37.5% (n= 39) had GDM at the time of study.

DISCUSSION

The overall finding of the present study showing no significant risk of GDM after infertility treatment is contradictory to the majority of previous studies in this research field. The vast majority of those studies assessed the risk of GDM among women undergoing fertility treatment to conceive. For example, Wang *et al*[32] found a 36% higher risk of GDM among Australian women who conceived after assisted reproductive technology (ART) than among women who conceived without ART. Similar findings were reported by Maman *et al* [41], who found that the risk of GDM was nearly double among women who conceived after ovulation induction alone or ART compared with women who conceived spontaneously. Two meta-analyses conducted to summarize the results of studies on ART and associated obstetrical complications showed a doubling of the risk of GDM after in vitro fertilization [21] and a 52% increased risk of GDM after fertilization with the use of intracytoplasmic sperm injection [42] compared with spontaneous conception.

In a prospective analysis by Tobias DK *et al*[43] in 40,773 eligible pregnancies, incident GDM occurred among 1,405 participants (5.2%) over 10 years of observation. A history of infertility was significantly associated with an increased risk of GDM. In the age-adjusted model, pregnancies among women with a history of infertility had a significant 50% higher GDM risk compared with those without such history (RR = 1.50, 95% CI: 1.34, 1.69) (*P*< 0.001). Adjustment for pre-pregnancy BMI and BMI change since age 18 years somewhat attenuated this relationship (RR = 1.38, 95% CI: 1.23, 1.55) (*P*< 0.001). Additional adjustment for additional pre-pregnancy lifestyle characteristics and GDM risk factors indicated that women with a pre-pregnancy history of infertility had a significant 39% greater risk of developing GDM compared with those without such history (RR = 1.39, 95% CI: 1.24, 1.57) (*P*< 0.001).

In a cross sectional study by Ashrafi M *et al*[31] compared the incidence of gestational diabetes mellitus between pregnancies conceived spontaneously and pregnancies conceived following assisted reproductive technology. The incidence of GDM was significantly higher in the IVF/ICSI and IUI groups (43% and 26%, respectively) compared with the spontaneous pregnancy group (10%).

In another cohort study conducted by Stern *et al*[44] to compare the risks for adverse pregnancy and birth outcomes by diagnoses with and without ART treatment to non-ART pregnancies in fertile women, they concluded that Gestational diabetes was increased for women with ovulation disorders (ART: 2.17(OR); non-ART: 1.94).

In a case control study by Reubinoff BE *et al*[45] comparing 260 women who conceived after IVF and 260 spontaneously conceived women, found that there were no statistically significant differences in the rate of GDM (p=0.16). In another case control study conducted by Tallo CP *et al* [46] comparing 101 IVF and spontaneously conceived pregnancies, the incidence of gestational diabetes was not statistically significant. A study by Koudstaal *et al* [35] assessing the pregnancy outcome following IVF pregnancies also gave similar results.

In a cohort study conducted by Jaques *et al* [47] in sub fertile conceiving without infertility treatment, there was weak evidence for gestational diabetes (adjusted OR 1.25, 0.96-1.63).

The present study is also consistent with the above studies suggesting no statistical significance in the incidence of GDM following infertility treated pregnancies compared to spontaneous conception group (p=0.69).

Prevalence Of Gestational Diabetes In Kerala

In a study by Mohan MA [48] at a tertiary hospital in North Kerala, the prevalence of GDM was estimated at 15.9%. The study showed higher prevalence of risk factors and complications such as age >25 years, BMI >26kg/m2, family history of DM, past history GDM, history of big baby, gestational hypertension, vaginal candidiasis, premature rupture of membranes and hyperbilirubinemia in GDM group as compared to non-GDM group. The study also demonstrated that modern life-style was a major influencing factor for development of diabetes in the study population.

In another study evaluating the prevalence of GDM on 700 antenatal patients attending a private hospital in Trivandrum by Paulose KP[49], the prevalence of GDM was 11.2%.

Another study by Sreekanthan K *et al* [50] on prevalence of GDM in Kollam district showed that the prevalence of GDM was 17%.

The prevalence of GDM in our study population turned out to be much higher (almost double) than that obtained in any other similar studies in Kerala (37.5%). This may be attributed to the high risk population seeking medical care at our institution and the high risk population in this part of Kerala.

Other Relevant Associations

There has been a statistically relevant increase in incidence of gestational diabetes in women with increasing age (53.6% in age group more than 30 years, while only 31.6% in women less than 30 years).

Strength Of The Study

i. This was the first study of its kind from South Kerala
ii. All the blood investigations were done from the in-house biochemistry laboratory which is accredited by National Accreditation Board for testing and calibration of Laboratories (NABL).
iii. Compared to other studies reviewed our study included 3 modes of infertility treatment.

Limitations Of The Study

i. We feel that the sample size was small to assess the statistical significance for the risk factors.
ii. The study population was not matched for confounders.
iii. The analysis was done for all three modalities of infertility treatment together- individual analysis was not done in view of small numbers involved.

CONCLUSION

Primary Outcome

The overall incidence of gestational diabetes in infertility treated women (39.6%) was comparable to that in spontaneously conceived women (35.6%) with singleton pregnancies, even though it was slightly higher but not statistically significant.

Secondary Outcome

The prevalence of gestational diabetes in our study population has been found to be 37.5%.

In addition, we have also found an increasing incidence of gestational diabetes within the age group more than 30 years.

REFERENCES

1. Sibai BM, Ross MG. Hypertension in gestational diabetes mellitus: pathophysiology and long-term consequences. The Journal of Maternal-Fetal & Neonatal Medicine. 2010 Mar 1;23(3):229-33.
2. Schneider H, Shaw J, Zimmet P. Guidelines for the detection of diabetes mellitus-diagnostic criteria and rationale for screening. The Clinical Biochemist Reviews. 2003 Aug;24(3):77–80.
3. Tundidor D, García-Patterson A, María MA, Ubeda J, Ginovart G, Adelantado JM, et al. Perinatal maternal and neonatal outcomes in women with gestational diabetes mellitus according to fetal sex. Gender medicine. 2012 Dec 1;9(6):411-7.
4. HAPO Study Cooperative Research Group. Hyperglycemia and Adverse Pregnancy Outcomes. New England Journal of Medicine. 2008 May 8;358(19):1991–2002.
5. Boney CM, Verma A, Tucker R, Vohr BR. Metabolic syndrome in childhood: association with birth weight, maternal obesity, and gestational diabetes mellitus. Pediatrics. 2005 Mar 1;115(3):e290-6.
6. England LJ, Levine RJ, Qian C, Soule LM, Schisterman EF, Yu KF, et al. Glucose tolerance and risk of gestational diabetes mellitus in nulliparous women who smoke during pregnancy. Am J Epidemiol 2004 Dec 15; 160(12):1205–13
7. Chu SY, Callaghan WM, Kim SY, Schmid CH, Lau J, England LJ, et al. Maternal obesity and risk of gestational diabetes mellitus. Diabetes Care 2007 Aug 1;30(8):2070–6.
8. Choi SK, Park IY, Shin JC. The effects of pre-pregnancy body mass index and gestational weight gain on perinatal outcomes in Korean women: a retrospective cohort study. Reprod Biol Endocrinol 2011 Dec;9(1):6.
9. Bener A, Saleh NM, Al-Hamaq A. Prevalence of gestational diabetes and associated maternal and neonatal complications in a fast-developing community: global comparisons. Int J Womens Health 2011;3:367–73.
10. Jones BJ, Zo¨llner J, Haynes S, Cheng F, Dornhorst A. In vitro fertilization treatment influences glucose tolerance in multiple pregnancy. Diabet Med 2013 Feb 1;30(2):252-4.
11. Hedderson MM, Ferrara A. High blood pressure before and during early pregnancy is associated with an increased risk of gestational diabetes mellitus. Diabetes Care 2008 Dec 1;31(12):2362–7.
12. Louis GM, Sundaram R, Schisterman EF, Sweeney AM, Lynch CD, Gore-Langton RE, et al. Heavy metals and couple fecundity, the LIFE Study. Chemosphere. 2012 Jun 1;87(11):1201–7.
13. Louis GM, Germaine M, Schisterman EF, Sweeney AM, Wilcosky TC, Gore-Langton RE, et al. Designing prospective cohort studies for assessing reproductive and developmental toxicity during sensitive windows of human reproduction and development—the LIFE Study. Paediatr Perinat Epidemiol. 2011 Sep 1;25(5):413–24.
14. Hull MG, Glazener CM, Kelly NJ, Conway DI, Foster PA, Hinton RA, et al. Population study of causes, treatment, and outcome of infertility. Br Med J (Clin Res Ed). 1985 Dec 14;291(6510):1693–7.
15. Wise LA, Rothman KJ, Mikkelsen EM, Sorensen HT, Riis A, Hatch EE. An internet-based prospective study of body size and time-to-pregnancy. Hum Reprod. 2009 Oct 14;25(1):253–64.
16. Rachon D, Teede H. Ovarian function and obesity—interrelationship, impact on women's reproductive lifespan and treatment options. Mol Cell Endocrinol. 2010 Mar 25;316(2):172-9. [PubMed]
17. Robker RL, Wu LL, Yang X. Inflammatory pathways linking obesity and ovarian dysfunction. J Reprod Immunol. 2011 Mar 1;88(2):142–8. [PubMed]
18. Linne Y. Effects of obesity on women's reproduction and complications during pregnancy. Obes Rev. 2004 Aug 1;5(3):137–43. [PubMed]
19. Grodstein F, Goldman MB, Cramer DW. Body mass index and ovulatory infertility. Epidemiology. 1994 Mar 1;5(2):247–50. [PubMed]
20. Tersigni C, Di Nicuolo F, D'Ippolito S, Veglia M, Castellucci M, Di Simone N. Adipokines: new emerging roles in fertility and reproduction. Obstet Gynecol Surv. 2011 Jan 1;66(1):47–63.
21. Jackson RA, Gibson KA, Wu YW, Croughan MS. Perinatal outcomes in singletons following in vitro fertilisation: a meta-analysis. Obstet Gynecol. 2004 Mar 1;103(3):551–63.
22. Shevell T, Malone FD, Vidaver J, Porter TF, Luthy DA, Comstock CH, Hankins GD, et al. Assisted reproductive technology and pregnancy outcome. Obstet Gynecol. 2005 Nov 1;106(5, Pt 1):1039–45.
23. Rani PR, Beegum J. Screening and diagnosis of gestational diabetes mellitus, where do we stand. J Clin Diagn Res. 2016 Apr;10(4):QE01-04.
24. Seshiah V, Balaji V, Balaji S, Sekar A, Sanjeevi CB, Green A. One step screening procedure for screening and diagnosis of gestational diabetes mellitus. J Obstet Gynecol India. 2005;55(6):525–9.
25. Mohan V, Mahalakshmi MM, Bhavadharini B, Maheswari K, Kalaiyarasi G, Anjana RM, et al. Comparison of screening for gestational diabetes mellitus by oral glucose tolerance tests done in the non-fasting (random) and fasting states. Acta Diabetol. 2014;51:1007–13.
26. Cozzolino M, Serena C, Maggio L, Rambaldi MP, Simeone S, Mello G, et al. Analysis of the main risk factors for gestational diabetes diagnosed with International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria in multiple pregnancies. J Endocrinol Invest. 2017 Sep;40(9):937-43.
27. Holst S, Kjær SK, Jørgensen ME, Damm P, Jensen A. Fertility problems and risk of gestational diabetes mellitus: a nationwide cohort study. Fertil Steril. 2016 Aug;106(2):427-34.
28. Jie Z, Yiling D, Ling Y. Association of assisted reproductive technology with adverse pregnancy outcomes. Iran J Reprod Med. 2015 Mar;13(3):169-80.
29. Xiao Q, Cui YY, Lu J, Zhang GZ, Zeng FL. Risk for Gestational Diabetes Mellitus and Adverse Birth Outcomes in Chinese Women with Polycystic Ovary Syndrome. Int J Endocrinol. 2016;2016:5787104. doi: 10.1155/2016/5787104. Epub 2016 Mar 14. PubMed PMID: 27066074; PubMed Central PMCID: PMC4808671.
30. Szymanska M, Horosz E, Szymusik I, Bomba-Opon D, Wielgos M. Gestational diabetes in IVF and spontaneous pregnancies. Neuro Endocrinol Lett. 2011;32(6):885-8.
31. Ashrafi M, Gosili R, Hosseini R, Arabipoor A, Ahmadi J, Chehrazi M. Risk of gestational diabetes mellitus in patients undergoing assisted reproductive techniques. Eur J Obstet Gynecol Reprod Biol. 2014 May;176:149-52.
32. Wang YA, Nikravan R, Smith HC, Sullivan EA. Higher prevalence of gestational diabetes mellitus following assisted reproduction technology treatment. Hum Reprod. 2013 Sep;28(9):2554-61
33. Huang LS, Yen CH, Lee SH, Shu BC, Lung FW, Kuo CP, et al. The pregnancy health and birth outcomes of women who underwent assisted reproductive technology: Results of a national survey. Iran J Reprod Med. 2011;9(4):269-76.
34. Venetis CA, Chambers GM. Maternal, pregnancy and neonatal outcomes following IVF pregnancies: An Evidence Check review brokered by the Sax Institute for NSW kids and Families;2015 Jun.
35. Koudstaal J, Braat DDM, Bruinse HW, Naaktgeboren N, Vermeiden JPW, Visse GHA. Obstetric outcome of singleton pregnancies after IVF: a matched control study in four Dutch university hospitals. Oxford J. Med Health Hum Reprod 2015 June;15(8):1819-25.
36. Tandulwadkar SR, Lodha PA, Mangeshikar NT. Obstetric complications in women with IVF conceived pregnancies and polycystic ovarian syndrome. J Hum Reprod Sci. 2014 Jan;7(1):13-8.
37. Retnakaran R, Qi Y, Connelly PW, Sermer M, Zinman B, Hanley AJ. Glucose intolerance in pregnancy and postpartum risk of metabolic syndrome in young women. J Clin Endocrinol Metab. 2010 Feb;95(2):670-7.
38. Sullivan SD, Umans JG, Ratner R. Gestational diabetes: implications for cardiovascular health. Curr Diab Rep. 2012 Feb;12(1):43-52.
39. Silverman BL, Rizzo T, Green OC, Cho NH, Winter RJ, Ogata ES, et al. Long-term prospective evaluation of offspring of diabetic mothers. Diabetes. 1991 Dec 1;40 (Suppl 2):121-5.
40. Reddy UM, Wapner RJ, Rebar RW, Tasca RJ. Infertility, Assisted Reproductive Technology and Adverse Pregnancy Outcomes: Executive Summary of a National Institute of Child Health and Human Development Workshop. Obstet Gynecol. 2007 Apr;109(4):967–77.
41. Maman E, Lunenfeld E, Levy A, Vardi H, Potashnik G. Obstetric outcome of singleton pregnancies conceived by in vitro fertilization and ovulation induction compared with those conceived spontaneously. Fertil Steril. 1998 Aug;70(2):240–5.
42. Pandey S, Shetty A, Hamilton M, Bhattacharya S, Maheshwari A. Obstetric and perinatal outcomes in singleton pregnancies resulting from IVF/ICSI: a systematic review and meta-analysis. Hum Reprod Update. 2012 Sep;18(5):485-503.
43. Tobias DK, Chavarro JE, Williams MA, Louis GM, Hu FB, Rich-Edwards J, et al. History of Infertility and Risk of Gestational Diabetes Mellitus: A Prospective Analysis of 40,773 Pregnancies. Am J of Epidemiol. 2013 Oct 15;178(8):1219–25.
44. Stern JE, Luke B, Tobias M, Gopal D, Hornstein MD, Diop H. Adverse pregnancy and birth outcomes associated with underlying diagnosis with and without assisted reproductive technology treatment. Fertil Steril. 2015 Jun;103(6):1438-45.
45. Reubinoff BE, Samueloff A, Ben-Haim M, Friedler S, Schenker JG, Lewin A. Is the obstetric outcome of in vitro fertilized singleton gestations different from natural ones? A controlled study. Fertil Steril. 1997 Jun;67(6):1077–83.
46. Tallo CP, Vohr B, Oh W, Rubin LP, Seifer DB, Haning RV. Maternal and neonatal morbidity associated with in vitro fertilization. The J of Ped. 1995 Nov;127(5):794–800.
47. Jaques AM, Amor DJ, Baker HG, Healy DL, Ukoumunne OC, Breheny S, et al. Adverse obstetric and perinatal outcomes in subfertile women conceiving

without assisted reproductive technologies. Fertil Steril. 2010 Dec 1;94(7):2674–9.
48. Mohan MA, Chandrakumar A. Evaluation of prevalence and risk factors of gestational diabetes in a tertiary care hospital in Kerala. Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2016 Apr;10(2):68–71.
49. Paulose KP. Prevalence of Gestational Diabetes in South Kerala. IMA Kerala Med J. 2008 Dec 30;1(2):49-51.
50. Sreekanthan K, Belicita A, Rajendran K, Vijayakumar A. Prevalence of Gestational Diabetes Mellitus in a Medical College in South India: A Pilot study. Indian J of Clin Practice. 2014 Sept;25(4):342-7.