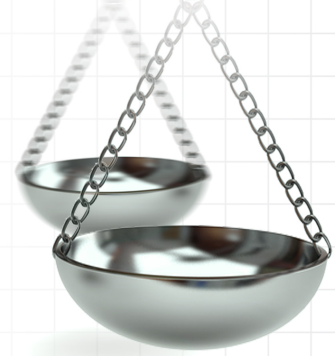
Research Article



Journal of Comparative Effectiveness Research

Comparing twice- versus four-times daily insulin in mothers with gestational diabetes in Pakistan and its implications

Background: Gestational diabetes mellitus is a common medical problem associated with maternal and fetal complications. Good glycemic control is the cornerstone of treatment. **Objective:** Compare outcomes between four times (q.i.d) and twice daily (b.i.d) regimens. The morning dose of the b.i.d regimen contained two-thirds of the total insulin, comprising a third human regular insulin and two-thirds human intermediate insulin; equal amounts in the evening. **Methods:** 480 women at >30 weeks with gestational diabetes mellitus with failure to control blood glucose were randomly assigned to either regimen. **Results:** Mean time to the control of blood glucose was significantly less and glycemic control significantly increased with the q.i.d regimen. Operative deliveries, extent of neonatal hypoglycemia, babies with low Agpar scores and those with hyperbilirubinemia were significantly higher with the b.i.d daily regimen. **Conclusion:** The q.i.d daily regimen was associated with improved fetal and maternal outcomes. Consequently should increasingly be used in Pakistan, assisted by lower acquisition costs.

First draft submitted: 31 March 2016; Accepted for publication: 12 May 2016; Published online: 14 July 2016

Keywords: fetal and maternal outcomes • gestational age • gestational diabetes mellitus • insulin • Pakistan

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Gestational diabetes mellitus (GDM) is defined as glucose intolerance during pregnancy. In most women who develop GDM, onset begins in the third trimester of pregnancy. Studies have recorded an incidence between 2 and 5% of pregnancies in the UK, with its prevalence rising [1]. A recent study conducted in Pakistan found a lower prevalence at <1% of pregnancies. In this study, the mean BMI and age were 24 kg/m^2 and 22 years, respectively, and all women were primigravida [2]. However, an earlier study by Akhter *et al.* showed a higher prevalence at 3.3% among Pakistani women [3]. Rates in the US appear higher, with GDM seen among 8–9% of all pregnancies, with rates potentially doubling in populations at high risk for Type 2 diabetes [4]. The highest prevalence of mothers with GDM are seen among south Asian and black Caribbean mothers, reaching up to 14% [5,6].

NICE in the UK currently recommends that women with potential risk factors including glycosuria, age >30 years, obesity, past history of GDM or glucose intolerance, or belonging to an ethnic group at high risk of GDM, be offered testing for GDM in the form of an oral glucose tolerance test [7].

The International Association of Diabetes and Pregnancy Study Groups recommends using a 'one-step' 75-g Oral Glucose Tolerance Test (OGTT) to diagnose GDM [8,9]:

- Time: plasma glucose;
- Fasting: ≥92 mg/dl (5.1 mmol/l);

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- 1 h: ≥180 mg/dl (10.0mmol/l);
- 2 h: ≥153 mg/dl (8.5 mmol/l).

The principal features of fetal and neonatal complications in pregnant women with GDM are macrosomia, neonatal hypoglycemia, perinatal mortality, congenital malformations, hyperbilirubinemia, polycythemia, hypocalcemia, and respiratory distress syndrome (RDS) in the newborn, marked by dyspnea with cyanosis. RDS usually occurs in newborn babies who are preterm, have diabetic mothers and who are delivered by cesarean section. However, sometimes there are no apparent predisposing causes [10–13]. Maternal complications include hypertension, pre-eclampsia, and an increased risk of a lower (uterine) segment cesarean section (LSCS) [14–16]. Hypoglycemia should be avoided as it can cause shakiness, nervousness, sweating, chills, irritability, confusion including delirium, rapid heartbeats, hunger and nausea, headache, fatigue, anger, nightmares, seizures and potentially unconsciousness.

Attempts to normalize blood glucose concentrations in pregnant mothers with GDM has become the cornerstone of treatment, with intensification of glucose monitoring as well as insulin administration improving perinatal outcomes [17,18].

No differences in neurodevelopmental outcome were seen in 2-year-old children born to mothers with GDM treated with insulin or metformin during pregnancy [19]. Most prospective trials involving insulin therapy in women with GDM have also shown a reduction in the incidence of neonatal macrosomia [17,20,21]. Mothers diagnosed with GDM should also have their blood pressure regularly monitored, undertake exercise and undergo nutrition counseling to help maintain normal glycemia levels. In patients with well controlled diabetes, there is no need to expedite delivery before 40 weeks of gestation. In mothers who require insulin, or have other co-morbid conditions, it is appropriate to begin antenatal screening with a nonstress test and an amniotic fluid index at 32 weeks gestation.

With respect to insulin therapy, our impression is that an insulin regimen administered four-times a day (q.i.d) is neither complicated nor more expensive, and may provide better outcomes for mothers and babies, compared with twice-daily (b.i.d) regimens. In addition, it may cost less. Such studies have been undertaken by other researchers in other countries [22,23]. However, we wanted to research this among a population in Pakistan since to the best of our knowledge such research has not been undertaken in this country before. Consequently, the objective of this study is to compare fetal and maternal outcomes of mothers with GDM receiving b.i.d versus q.i.d insulin regimen when diet and exercise had failed to control blood glucose levels over 1–2 weeks. Subsequently, use the findings to provide future direction and guidance to key stakeholder groups in Pakistan.

Methods

This quasi-experimental study was conducted prospectively from June 2014 to September 2015 in the Obstetric ward at Holy Family Hospital (Rawalpindi, Pakistan). The Holy Family Hospital is the biggest hospital in the region serving a population of 5 million for antenatal care, and undertaking approximately 100–150 deliveries daily.

We calculated based on previous studies, coupled with the limitation of only conducting this study in a single hospital and an envisaged informed consent rate of approximately 50%, that we needed to approach 1000 mothers with GDM meeting the inclusion criteria for their consent to take part in the study.

Inclusion criteria included a singleton gestation and gestational age of 30 weeks or above. Random blood glucose (RBG) testing as well as fasting blood glucose (FBG) levels were used to diagnose GDM. GDM was determined as follows: 100 g oral glucose ingestion followed by at least two serum glucose concentration values ≥5.9, 10.6, 9.2, 8.1 mmol/l at 0, 1, 2 and 3 h, respectively, or by the 75 gm oral glucose tolerance test using the International Association of Diabetes and Pregnancy Study Groups criteria for diagnosis of GDM – the one step 75 gm OGTT [8,9] – with similar levels at fasting and 2 h. Additional tests included glycosuria (++) on urine examination, abnormal glycosylated hemoglobin (>6.1%) and booked as well as nonbooked patients.

Mothers with congenital anomalies of their fetus and having other medical disorders including pre-existing diabetes were excluded from this study.

After informed consent, the mother's history was taken. This included their age, parity, gestational age, and the presence of any other associated maternal diseases. There was also a general physical examination, which included their blood pressure, pulse, temperature and respiratory rate. The abdominal examination included the fundal height, lie of the fetus and its presentation as well as the fetal heart sounds.

Details regarding the mother's complete blood picture, chemistry, FBG, 2 h postprandial, 2 h postlunch, 2 h postdinner, urinalysis and HbA1C levels were also obtained prior to delivery. Fetal monitoring was carried out via a fetal kick count chart. There were also serial ultrasounds scans to determine the extent of fetal growth. A biophysical profile and an amniotic fluid index score were also performed. Severe maternal hypoglycemia was particularly noted.

Table 1. Mean time (h) taken to control blood glucose levels.

Glycemic control	n	Mean	Standard deviation	p-value
4.4–5.3 mmol/l (four times regimen)	192	6.500 ± 0.33	1.6418 ± 0.3351	0.001
More than 5.3 mmol/l (twice daily regimen)	288	9.694 ± 0.37	2.2016 ± 0.3669	

The main fetal outcome measures were Apgar scores at 0 and 5 min, presence of hypoglycemia, extent of glycemic control, presence of hyperbilirubinemia and birth weight. The main maternal outcome measures included hypoglycemia, extent of glycemic control, mean time taken in both regimens to control blood glucose level and the extent of operative deliveries.

Insulin regimen & dietary recommendations

Mothers who failed to have their blood glucose levels controlled on diet and exercise were randomly assigned to receive either the b.i.d or q.i.d insulin regimen by means of a computer-generated random table.

For mothers allocated to the b.i.d regimen, the morning dose contained two-thirds of their total daily insulin with the afternoon dose the remainder. The morning dose comprised a third human regular insulin (Actrapid®, Novo Nordisk, Australia) and two-thirds human intermediate insulin (Insulated™, Novo Nordisk), with the evening dose comprising equal amounts of regular and intermediate insulin.

Insulin was started with a minimum dose of 10 units. Adjustments to the insulin dose were subsequently individualized for the total amount of insulin as well as the ratios between the insulins according to the mothers' response. For mothers allocated the q.i.d insulin regimen, the first three doses of regular insulin were given by insulin pen (NovoPen® 3, Novo Nordisk) half an hour before each main meal, and the fourth dose of intermediate insulin was given before bed time.

The dietary recommendations for all women were 0.13–0.15 MJ/kg of their ideal bodyweight, given as three meals and three snacks daily, comprising 55% carbohydrate, 20% protein and 25% fat, with increased complex and decreased refined carbohydrates.

Glycemic control

Glycemic control was assessed by glucose monitoring and by monthly measurements of HbA1C. Capillary whole blood glucose was measured by the glucose kinase methods when women were admitted to hospital and by self-monitoring glucose reflectance meters at home (Accutrend, Accu-Chek, Roche, Switzerland). Values were verified by the glucometer's memory.

In both groups, six measurements were taken daily until adequate control was achieved. Thereafter, measurements were taken monthly for 3 months or until the baby was delivered. Goals for glycemic control were blood glucose concentration of 3.5 – 5.9 mmol/l before meals [22], 6.7 mmol/l or less 2 h after meals and mean daily values of 4.4–5.3 mmol/l. The upper values served as the threshold for initiation of insulin or an increase of the dose. Mean glucose levels were calculated over an 11 h period.

The aim for HbA1C concentration was below 6%. Hypoglycemia was characterized by abnormally low blood glucose levels <70 mg/dl. Severe maternal hypogycemia was characterized by blood glucose levels of 35–40 mg/dl, and can lead to confusion, disorientation, convulsions, fitting, seizures, intense nightmares whilst asleep and loss of consciousness and coma. This typically requires assistance from another person to treat.

Delivery

An important objective was for the fetuses to be delivered at term. The timing of any induction of labor was determined by an overall assessment of maternal and fetal risk factors including poor compliance, suboptimal glycemic control, vasculopathy, macrosomia, suspicious fetal biophysical test and a poor obstetric history. Patients with an uncomplicated GDM and an unfavorable cervix were allowed to wait until spontaneous onset of labor. Delivery was induced if there was a favorable cervix at 38–41 weeks gestation or if the patient had not delivered by 41 weeks. Treatment was individualized for those women with gestational diabetes whose pregnancy was complicated. The aim for glucose concentration was 4–5 mmol/l during labor and delivery.

At delivery, the neonate was attended by the neonatal staff with Agpar scores determined at 0 and 5 min.

Table 2. Extent of glycemic control.

Glycemic control	q.i.d (n)	b.i.d (n)	Total (n)	Chi² test	p-value	Likelihood ratio	p-value	df
4.4–5.3	176	16	192	222.22	0.001	250.17	0.001	1
>5.3	64	224	288					
Total	240	240	480					

b.i.d: Twice daily; df: Degree of freedom; q.i.d: Four times daily.

Table 3. Maternal hypoglycemia.

Maternal hypoglycemia	q.i.d (n)	b.i.d (n)	Total (n)	Chi² test	p-value	Likelihood ratio	p-value	df
Yes	192	80	272	106.43	0.001	111.14	0.001	1
No	48	160	208					
Total	240	480						

b.i.d: Twice daily; df: Degree of freedom; q.i.d: Four times daily.

Blood samples were taken six times during the first day of life for measurement of plasma glucose concentration, and serum bilirubin was measured 1–3 times from the first day of life. Serum bilirubin up until 1 mg/dl was seen as normal with RBG levels until 40 mg/dl seen as normal as well. If indicated, neonates were admitted to neonatal intensive care unit for dextrose infusion or phototherapy.

Data analysis

All information collected was recorded in a predesigned questionnaire. The data were entered on SPSS Version 10 for statistical analysis. Student's t-test was used to compare mean time taken to control blood glucose levels, and Chi-square test was used for glycemic control, operative deliveries, Apgar Scores, birth weight, neonatal hypoglycemia and hyperbilirubinemia. Statistical significance was assigned to p-value <0.05. The variables studied included gestational age in weeks, mean time taken to control blood glucose levels, glycemic control, mode of delivery and neonatal outcome such as Apgar Scores, birth weight, neonatal hypoglycemia and hyperbilirubinemia.

The study was approved by the bioethical committee of the hospital and assigned protocol No. BEC-GAO-HFH-1134.

Results

A total of 480 mothers were eventually recruited, equating to a 48% acceptance rate. 240 mothers with GDM subsequently received the b.i.d insulin regimen and 240 received the q.i.d insulin regimen.

The mean age of the mothers with GDM was 32 ± 6 years, with gestational ages more than 30 weeks (term pregnancies). The BMI of the mothers was between 29 and 35. There were few primigravida with most mothers being mutipara having three or more children. Baseline glycemic levels were: fasting >110 mg/dl, postprandial >140 mg/dl and baseline HbA1C levels >6.1%. There were no significant differences in the case mix of the groups of mothers and in the frequency of background factors known to be associated with adverse outcomes of pregnancy.

All were term pregnancies at more than 37 weeks of gestation with no premature deliveries. The mean birth weight was 3.45 kg with no small for gestational age babies and no large for gestational age babies. There was no macrosomia, no intrauterine deaths, no pregnancy-induced hypertension and no pre-eclampsia.

The mean time interval to the control blood glucose levels is shown in Table 1. Overall, the mean time taken to control blood glucose levels was significantly less in patients who received the q.i.d regimen compared with those who received b.i.d insulin regimen (p = 0.001; Table 1).

Glycemic control as reflected in the mean daily concentration of glucose (Table 2) was significantly better with the q.i.d insulin regimen compared with the b.i.d regimen (p = 0.001; Table 2). In total, 176 mothers who received the q.i.d regimen had better glycemic control compared with only 16 mothers who received the b.i.d regimen (73.3 vs 6.6%). In addition, only 64 mothers did not achieve glycemic control in the q.i.d regimen compared with 184 with the b.i.d regimen.

A higher mean dose of insulin was given to mothers who received insulin q.i.d; however, without an increase in episodes of severe maternal hypoglycemia. In total, 192 patients in the q.i.d regimen group had an episode of hypoglycemia during the course of the study compared with 80 patients in the b.i.d regimen group (p = 0.001; Table 3; 80 vs 33.3%). However, overall glycemic control was improved in the q.i.d regimen group (Table 2).

Table 4. Mode of delivery.

MoD	q.i.d (n)	b.i.d (n)	Total (n)	Chi² test	p-value	Likelihood ratio	p-value	df
Svd	168	104	272	43.06	0.001	49.51	0.001	2
LSCS	72	120	192					
Instrumental	0	16	16					
Total	240	224	480					

b.i.d: Twice daily; df: Degree of freedom; LSCS: Lower cesarean section; MoD: Mode of delivery; q.i.d: Four times daily; Svd: Spontaneous vaginal delivery.

Table 5. The extent of hypoglycemia in neonates.

Hypoglycemia	q.i.d (n)	b.i.d (n)	Total (n)	Chi² test	p-value	Likelihood ratio	p-value	df
<40	16	136	152	138.64	0.001	153.36	0.001	1
>40	224	104	328					
Total	240	240	480					

b.i.d: Twice daily; df: Degree of freedom; q.i.d: Four times daily.

A statistical difference was found between the two groups regarding the method of delivery (Table 4) with 72 mothers in the q.i.d regimen undergoing LSCS compared with 120 patients in b.i.d regimen. However, there was no difference in the extent of pregnancy induced hypertension between the two insulin groups.

Among the women with GDM receiving the b.i.d regimen, emergency cesarean sections were performed in 30%, with 20% elective. The indications for elective cesarean sections were two or three previous scars.

Tables 5–7 summarize the neonatal outcome data. In neonates born to mothers with GDM, the most prevalent complications of hypoglycemia and hyperbilirubinemia were lower in neonates whose mothers received the q.i.d regimen compared with the b.i.d regimen.

A total of 16 babies in the q.i.d regimen group had hypoglycemia versus 136 in the b.i.d regimen group hypoglycemia (6.6 vs 56.6%), which was statistically significant (p = 0.001). In total, 224 neonates did not have hypoglycemia in the q.i.d regimen, compared with only 104 neonates in the b.i.d regimen (p = 0.001) (Table 5).

A total of 40 neonates in the q.i.d regimen group had hyperbilirubinemia versus 136 in the b.i.d group (16.6 vs 56.6%), which was statistically significant (p = 0.001). In total, 200 neonates did not have hyperbilirubinemia in the q.i.d group compared with 104 in the b.i.d regimen group (p = 0.001) (Table 6).

There was a statistically significant difference in the Apgar scores (A/S) of neonates (Table 7) between the two regimens. In total, 224 neonates in the q.i.d regimen group had a A/S >7/10 versus 68 in b.i.d regimen, which was statistically significant (p = 0.001). Sixteen neonates in q.i.d group had A/S <7/10 compared with 104 babies in b.i.d group.

There was no statistically significant difference in birthweight of babies born to mothers in either group, with an average weight of 3.4 ± 0.269 kg.

Discussion

In this study, intensive blood glucose monitoring as well as various other factors were used to evaluate which of the two insulin dose regimen would provide better overall outcomes for both mothers and babies in mothers with GDM.

With respect to the babies born, mothers with GDM who received the q.i.d insulin regimen had a significant reduction in the rate of neonatal hypoglycemia (6.6 vs 56.6%; Table 5), and hyperbilirubinemia (16.6 vs 56.6%; Table 6) versus those mothers administering the b.i.d regimen. The reduction in the rate of both hypoglycemia and hyperbilirubinemia among neonates resulted from the significant improvement in glycemic control in mothers (73.3 vs 6.6%; Table 2). This, in turn, resulted from an increase in the mean dose of insulin administered. Our findings are in agreement with those of others [24–28] who found that administrating the q.i.d regimen in pregnancy improved glycemic control and perinatal outcomes without risk to the mother except for hypoglycemia. However, this did not lead to severe hypoglycemia. In our study, women who received the q.i.d regimen also had more episodes of hypoglycemia (Table 3). However, glycemic control was improved in the q.i.d regimen (Table 2), and overall there was no difference in the birthweight of infants with either regimen. This was in agreement with the study by Price *et al.* [29], although contrasted with the findings of de Veciana *et al.* [30]. These authors found that the q.i.d regimen did lead to a further reduction in the incidence of large babies, that is, with birth weights greater than 4 kg or a birthweight greater that the 90% centile.

Overall, this study showed that the q.i.d regimen of insulin provided a significantly better outcome for mothers with GDM in terms of a significantly greater chance of a vaginal delivery, and a correspondingly lower chance of an instrumental delivery or LSCS (Table 4). Neonates also had significantly higher Agpar

Table 6. Hyperbilirubinemia among neonates.

Extent of hyperbilirubinemia	q.i.d (n)	b.i.d (n)	Total (n)	Chi² test	p-value	Likelihood ratio	p-value	df
>1	40	136	176	82.68	0.001	86.17	0.001	1
<1	200	104	304					
Total	240	240	480					

b.i.d: Twice daily; df: Degree of freedom; q.i.d: Four times daily.

Table 7. Apgar score of neonates.

Agpar score	q.i.d (n)	b.i.d (n)	Total (n)	Chi² test	p-value	Likelihood ratio	p-value	df
>7/10	224	136	360	86.04	0.001	93.84	0.001	1
<7/10	16	104	120					
Total	240	240	480					

b.i.d: Twice daily; df: Degree of freedom; q.i.d: Four times daily.

scores and a significantly lower chance of hyperbilirubinemia (Tables 6 & 7). The improvements in outcomes with the q.i.d regimen is in agreement with the findings of Konje *et al.* [22]. The q.i.d regimen was also marginally less expensive at 789PKR (US$7.44) versus 799PKR (US$7.53) for the b.i.d regimen. In addition, the q.i.d regimen contains only one type of insulin. This contrasts with the b.i.d regimen where there are frequent changes in the ratio of each injection, which can be cumbersome for the patient. This finding is in agreement with the those of Nachum *et al.* [24].

We are aware that our study was carried out within a single hospital in Pakistan. However, we believe that in view of the large number of mothers with GDM enrolled, and the highly significant results that we saw in a number of key maternal and fetal outcome parameters between the two regimens, that the findings should be applicable to other women with GDM in Pakistan. We are also planning further studies to substantiate the observations seen as well as look at different ratios of insulin in the b.i.d regimen, for example, 50:50, to see if our conclusions still hold.

Conclusion

The results of this study suggests that compared with the b.i.d insulin regimen, the q.i.d insulin regimen for GDM patients results in significantly improved fetal and maternal outcomes across a range of measures including reduced operative deliveries alongside improved Agpar scores of babies, neonatal hypoglycemia and neonatal hyperbilirubinemia. The q.i.d regimen may be associated with greater maternal hypoglycemia; however, this was not severe enough to cause symptoms and overall glycemic control was significantly better with the q.i.d regimen. As a result, the q.i.d regimen should increasingly be used in Pakistan, assisted by lower costs. We will be looking to substantiate this in future studies including future studies with different insulin ratios for the b.i.d regimen.

Acknowledgements

The authors strongly acknowledge the support of the mothers who participated in this study, along with physicians, staff attendants and the laboratory staff of the Holy Family hospital who gave their time and expertise to assist with this study. The authors also thank the hospital for providing the funds to procure the medicines for this study.

Financial & competing interests disclosure

The write-up of this study was in part sponsored by the Karolinska Institutet. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

Executive summary

- Gestational diabetes mellitus (GDM) is a common medical problem worldwide, with mothers from South Asia and black Caribbean women at particular risk with a prevalence up to 14% of all mothers.
- All women with risk factors for GDM should be offered 2-h 75 gm Oral Glucose Tolerance Test at 24–28 weeks of pregnancy. Women, who have had GDM in a previous pregnancy, should be screened much earlier, at 16–18 weeks.
- Patients not meeting fasting blood sugar <95 mg/dl and 2-h postprandial blood glucose levels <120 mg/dl with dietary changes should begin insulin therapy.
- Antenatal screening should begin in such patients at 32 weeks with nonstress test and amniotic fluid index with infants to be delivered at term.
- Four-times regimen results appear to be significantly better in terms of fetal and maternal outcomes across a range of measures as compared with a twice-daily insulin regimen. These include the extent of maternal glycemic control, mode of delivery as well as the extent of hypoglycemia and hyperbilirubinemia in neonates and their Agpar scores.

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