M : , H J : , M : A B - *

Background: D L (L).

Methods: A J- 2010 . A . M - CHE G - G ADE

Results: A 70 (24 28) . I ( ) - (3 - : 3791 , , ,) - ( ) (=0.20; 95% CI: 0.03-1.10) (' ' -). - - (2 - : , 5286 , , , : =0.40, 95% CI 0.25- 0.63), - - (3 - : , 2469 , , , : =0.51, 95% CI 0.14-1.88). (,) - (3 - : : 910 , , ,) (=0.29, 95% CI 0.14 -0.60) D , 10% : - .

Conclusions: D , , - - - - D , 10% : - , L .

With increasing prevalence of diabetes, the prevalence of diabetes complicated pregnancies is also increasing. Normally, as the pregnancy progresses, mothers experience lower glucose levels compared to the non pregnant state. With the progression of pregnancy there is lowered glucose tolerance, increasing glucose and insulin levels. Although this is a normal physiological process, it can become pathological in 3-6 % pregnancies [1]. Gestational diabetes is defined as any degree of glucose intolerance with onset or first recognition during pregnancy [2]. A woman can also be diabetic prior to pregnancy and that falls into two categories: type 1and type 2. Type 1 diabetes occurs due to a lack of pancreatic islet beta cells,

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caused by autoimmune destruction and resulting in an absence of insulin; while type 2 diabetes occurs due to insulin resistance and beta cell dysfunction and is likely to be the result of interactions between genetic, environmental and immunological factors including diet, physical activity and obesity [3]. Women diagnosed with diabetes prior to pregnancy (pre-existing diabetes) will experience an increase in insulin demands during pregnancy [4].

Diabetes can have significant impacts on maternal, fetal and neonatal outcomes. The presence of diabetes can

Data abstraction

The data were extracted by two researchers into a standard Web excel sheet prepared by the CHERG/LiST review group [8]. The variables considered included, for example, location of the study, setting, study design, blinding assessment, allocation concealment, intention-to-treat analysis, lost to follow-up rates, intervention and control group definitions and study limitations.

Study characteristics and quantitative data synthesis

The study designs considered were randomized, quasi-randomized trials and observational studies. We generated meta-analyses using RevMan 5.0 software for

95% CI 0.14-6.77). A retrospective cohort study by Traub et al.1987 [72] compared treatment in peripheral maternity units with hospital based (centralized) treatment. No difference in effect on rates of stillbirth were noted (RR=0.42, 95% CI 0.09-2.01).

(3) Intensified management (dietary advice, monitoring or pharmacotherapy) versus no or conventional management strategies for diabetes in pregnancy

A number of studies have focused on the impact of monitoring and treatment of diabetes in pregnancy versus no care/conventional care. In our review one study [15] studied the impact of intensive monitoring versus routine monitoring of serum glucose levels in a population of pregnant women with impaired glucose tolerance. The intervention group received dietary advice, capillary blood glucose monitoring five times a week and HbA1c measurements monthly, wheras the routine monitoring group received dietary advice and monthly HbA1c measurement. No stillbirths were reported in either comparison group. This was the only study which assessed the effect of monitoring of glucose levels in women with impaired glucose tolerance in pregnancy.

Four intervention studies [13,23-25] with randomized design assessed the same comparison of intensified versus conventional management in women with GDM. Pooling of results from these three studies displays an 80% non-significant reduction in risk of stillbirth (RR=0.20, 95% CI: 0.03- 1.10) when intensive management protocols are utilized (figure 2). Of these studies, Langer et al. 1994 focused on assessing the effect of intensified monitoring (7 checks of serum glucose/day) versus conventional monitoring in a group of women with gestational diabetes. This was coupled with treatment as dictated by serum glucose levels. A non significant effect was seen on risk of stillbirths (RR=0.23, 95% CI 0.03-1.97) and neonatal mortality (RR=1.49, 95% CI 0.23- 5.68). A randomized controlled trial by Crowther et al. 2005 consisting of 1031 subjects, reported a non-significant impact on the risk of perinatal mortality (RR = 0.09; 95% CI: 0.01 – 1.70) when gestational diabetics received individualized dietary advice, serum glucose monitoring and insulin therapy compared to routine care. Three stillbirths were reported in the routine care group (p-value 0.25). A similar trial by Garner et al 1997 conducted on patients with GDM comprising a small sample size (300 subjects) did not report any stillbirths. An RCT conducted by Landon et al. 2009 [25] focused on intensive treatment of gestational diabetes versus conventional management. It did not report any perinatal deaths in either groups but displayed positive effect of intervention on risk of large for gestational age (LGA), shoulder dystocia, need for cesarean section, gestational hypertension and pre eclampsia. Table 1 gives the quality grading of the outcome(s) according to the CHERG rules.

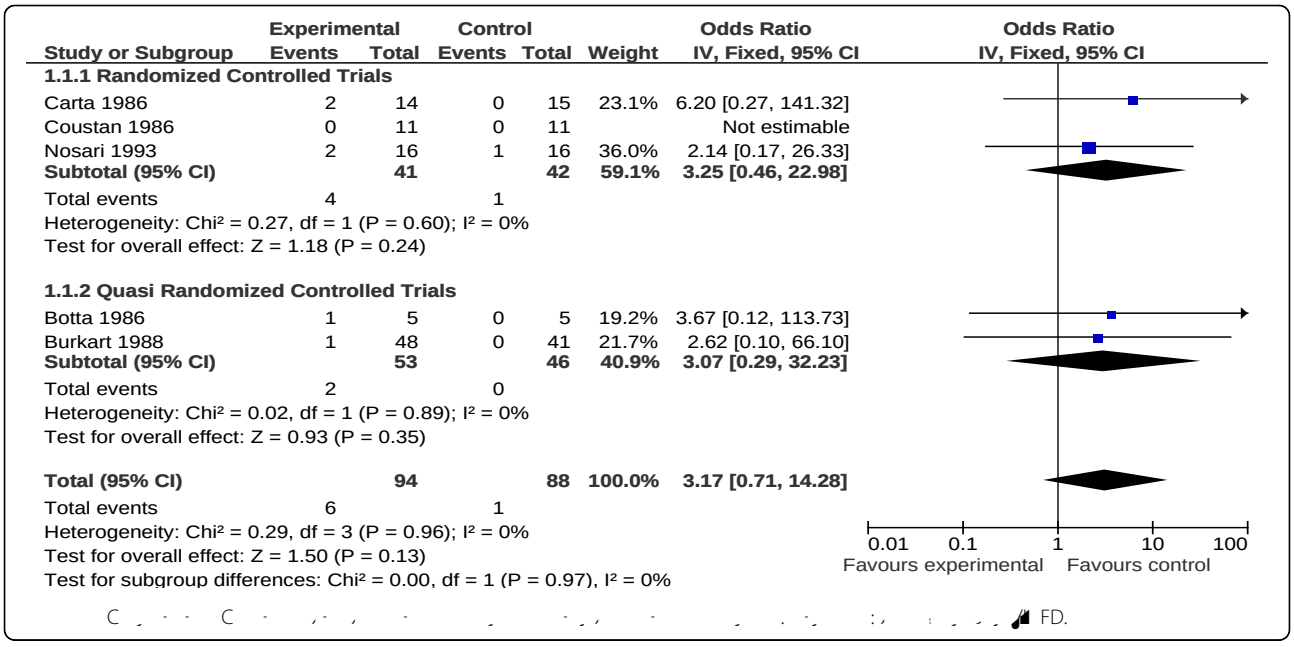
Observational studies which looked at similar comparisons were also identified [28,32,33,35,49,50,75]. A cohort study by Huddle et al. (2005) [50] focused on pregestational and gestational diabetes in a population of black

women. Initial hospitalization, intensive monitoring and management in one group were compared to only two weeks of intensive management in the group that

(6) The effectiveness of continuous infused insulin versus multiple dose insulin

Seven studies focused on the comparison of continuous subcutaneous insulin versus conventional multiple injections of insulin. Six of these studies were intervention studies [16-21] and one was an observational study [47].

Of the six intervention studies [16-21] five were on type 1 diabetics and one included both type 1 and 2 dia-



insulin aspart versus human insulin on stillbirths did not show significant effect on the risk of stillbirth (RR=1.05, 95%CI 0.07-16.7).However, there were only 322 subjects in this trial. Persson et al. 2002 [22] studied the effects of insulin Lispro versus regular insulin. There were no stillbirths or neonatal deaths reported in this comparison. A single observational study by Aydin et al.2008 [78] assessed the comparison of insulin lispro versus regular human insulin and did not report a significant difference in on the risk of stillbirth (RR=2.14, 95% CI 0.14-33.03). Whereas the other prospective cohort [63] compared the effects of glargine versus NPH insulin. There were two stillbirths reported in the group of pregestational diabetics using NPH insulin and none in the glargine utilizing group (p-value=0.028).

(8) Oral hypoglycemic agents and metformin use in diabetic pregnancies

Five observational studies [39,46,48,51,65] focused on the impact of using oral hypoglycemic agents or metformin versus diet alone or insulin. Of these studies Holt et al. 2008 [48] compared the effect of glibenclamide versus insulin in a population of women with GDM. No significant difference was seen on risk of stillbirth (RR= 3.07, 95%CI 0.13-73.31). A retrospective cohort study by Ekpebegh et al 2007 [39]compared women treated with oral glucose-lowering agents (OGLA-metformin and glibenclamide) alone (group 1) and women converted from OGLA to insulin (group 2) with women who were treated with insulin alone and women converted from diet to insulin (group 3). There was a significant difference in perinatal mortality rates between group the three groups; perinatal mortality rates (per 1000 births): 125, 28 and 33 (p-value=0.003). At least one group differed significantly from another (p-value=0.003). It is clear that the PNM rate for those on OGLA alone, 125 per 1000, was much higher than for the other two groups. The majority of all perinatal deaths were stillbirths: eight of 11 in the OGLA alone group and five of seven in the OGLA to insulin group.

A study by Hughes et al 2006 [51] compared use of metformin versus none in type 2 diabetics. No significant difference was observed in perinatal loss (p-value =0.65). Another retrospective cohort study Rayburn et al 2006 [65] compared pregnancies requiring oral hypoglycemic drugs with those controlled with diet alone. A single stillbirth was reported in the diet controlled group with none in the treatment group and the results were not significant. Hellmuth et al. 2007 compared metformin with sulphonylureas in pregnant diabetic patients and a reference group treated with insulin.

(9) Pregestational and gestational DM versus normal pregnancy

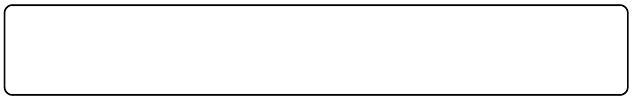
Our literature search also yielded studies which assessed the risk of stillbirth in the above mentioned comparison. Twelve observational studies assessing the risk of stillbirth in pre-gestational and gestational diabetes versus normal pregnancies [82-93] were identified. Of these, five studies [82-86] could be pooled to assess risk of stillbirth in women with diabetic pregnancy versus normal women. Pooled data from these studies displayed a significant effect on stillbirth risk in the fixed effects model (RR 2.17, 95% CI 1.45-3.25). Due to considerable heterogeneity

I^2=95% and p-value <0.10, a random effects model was also applied which indicated that the results were statistically insignificant (RR=3.38, 95%CI 0.49-23.34).

Delphi results

Figure 6 summarizes the estimates (medians) from the Delphi consensus for the effect of intervention of dia-

urinary tract disorder, macrosomia, birth injury, and perinatal mortality. These risks can be minimized by optimal glycaemic control, both prior to and throughout the pregnancy [98,99], and this is best achieved through comprehensive preconception care where other issues such as genetic risks, health status, reproductive history, exposure to environment toxins, immunization and life-style risk factors can be addressed via a community based approach to manage diabetes before and during pregnancy [100].



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