Should pregnant women be excluded from community based lifestyle intervention trial?- a case study

Elezebeth Mathews, Ph.D., MPH

Assistant Professor

Department of Public Health and Community Medicine

Central University of Kerala, India.

Background

- India - Second largest type 2 diabetes mellitus (T2DM) population (Shaw et al. 2009)
- Kerala - highest prevalence rates among Indian states (Kutty et al. 1999)
- Large efficacy trials – Proves risk of developing T2DM can be reduced by 60% following lifestyle changes (Tuomilehto et al. 2009, Kosaka et al. 2005, Knowler et al. 2002, Ramachandran et al. 2009, Li et al. 2008)
- Gestational diabetes or GDM (High blood sugar in pregnancy) - increasing worldwide (Metzger 1998)
- GDM prevalence in India - 16.55 %(Seshiah et al. 2004), lowest- 3.8% reported in Jammu (Zargar et al. 2004) highest- 17.8% in Tamil Nadu (Seshiah et al. 2008)

- GDM - Long term and short term health risks for the pregnant woman, her fetus, and child's future.
- Pregnant woman- gestational hypertension (Bryson et al. 2003), pre-eclampsia , higher risk for T2DM in future
- Child - Macrosomia, neonatal complications and birth defects (Mitanchez et al. 2010)
- Child – Future risks - childhood obesity and glucose intolerance in early adulthood (Hillier et al. 2002).
- Trans-generational cycle of 'diabetes-begets-diabetes' (Clausen et al. 2008, Egeland et al. 2000)

Case Study-A cluster randomized controlled trial of a lifestyle intervention program to compare life style intervention versus no intervention

- Aim - to estimate the effectiveness of a culturally adapted lifestyle intervention in reducing the incidence of T2DM among high-risk individuals.
- Sample selection criteria-
  - Individuals with a diabetic risk score greater than 60
  - Who were either normoglycemic, having impaired fasting glucose (fasting plasma glucose concentration of ≥100 and <126 mg/dl)) or impaired glucose tolerance (2hr plasma glucose concentration of ≥140 and <200 mg/dl)
  - Exclusion criteria - prior diagnosis of T2DM, myocardial infarction, heart failure, stroke, cancer, epilepsy, arthritis or dementia, current use medications known to affect glucose tolerance (glucocorticoids, anti-psychotic drugs, and anti-retroviral drugs) and **pregnancy**

Possible reasons for exclusion

(i) As per the Indian Council of Medical Research(ICMR) "Ethical Guidelines For Biomedical Research on Human Participants" pregnant women are considered as "special group" (ICMR 2006)

(ii) A strong possibility of the community attributing any complications that might arise during pregnancy to the trial.

(iii) Cultural practice of transient migration of pregnant women to their mother's house for delivery – risk of loss to follow up

(iv) A different Diabetic risk score for pregnant women is different for the general population

Ethical concerns: Favorable benefit-harm ratio

- Participation might have facilitated better health outcomes for the woman, her fetus and future child.
- Could also have contributed to a better understanding of the short- and long-term effects of lifestyle modification on these populations
- Exclusion deprived pregnant women of the benefits of screening for high-risk status, and subsequent potential involvement in the lifestyle modification intervention.
- Presence of the risk factors and the “high risk-status” leads to gestational diabetes among pregnant women rather than the state of “pregnancy”-primary research outcome of the study is unaffected on inclusion.

Ethical concerns: Fair inclusion exclusion criteria

- Pregnant women should have been eligible for inclusion in the trial.
- Reasonable alternatives to exclusion:
  - Enrolling pregnant women until the first trimester of pregnancy
  - Adopting a screening tool that is valid for pregnant women
  - Could have been screened for the high-risk status and given an opportunity to make an informed decision about research participation
- Legitimate exclusion could have been restricted to pregnant women with high blood glucose levels suggestive of gestational diabetes as per the standard criteria.

Community perspectives and experiences regarding pregnancy

- Four lifestyle interventions that lower risk of gestational diabetes- smoking cessation, regular physical activity, healthy body weight, and a healthy diet (Solomon et al. 1997, Tobias et al. 2012, Zhang et al. 2006)
- Tobacco use is very low among women in Kerala.
- In India, it is widely believed that pregnant women should consume high calorie, energy dense food-to meet the needs of the pregnant women and the growing foetus, and restrain from any form of physical activity- thought to cause loss of pregnancy.
- Myths and taboos increase the risk of pregnant women developing gestational diabetes or diabetes thereafter.
- Participation in a trial on adapted lifestyle interventions could have helped to challenge these myths and taboos.

Commentary and recommendations for future research

- Most Non-communicable diseases have their onset in the womb, influenced further by environmental exposures.
- Unjustified exclusion of pregnant women
  - Being part of the trial would have benefitted the pregnant woman, her fetus, and subsequent generations, with no foreseeable harm.
  - Limits exploration and advancement of research on future disease prevention in the population at large.
- Empowering the community and pregnant women to weigh the benefit for the mother and baby versus risk of participation in the trial
- Community perspectives on pregnancy might make the inclusion of pregnant women with no “visible health problem” in trials a challenge. This fact will have to be considered while formulating a policy in this regard.
- A recommendation is for research funding organizations and ethical review boards to insist on justification(s)for exclusion of pregnant women from research.

References

1. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes Res ClinPract. 2010; 87(1):4-14. doi: 10.1016/j.diabres.2009.10.007. Epub 2009

2. Raman Kutty V, Joseph A, Soman CR. High prevalence of type 2 diabetes in an urban settlement in Kerala, India. Ethn Health. 1999 ;4(4):231-9

3. Tuomilehto J, Lindström J, Eriksson JG, Valle TT, Hämäläinen H, Ilanne-Parikka P, Keinänen-Kiukaanniemi S, Laakso M, Louheranta A, Rastas M, Salminen V, Uusitupa M, Finnish Diabetes Prevention Study Group: Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med 2001, 344:1343–1350.

4. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM, Diabetes Prevention Program Research Group: Reduction of the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002, 346:393–403.

5. Kosaka K, Noda M, Kuzuya T: Prevention of type 2 diabetes by lifestyle intervention: a Japanese trial in IGT males. Diabetes Res ClinPract 2005; 67:152–162.

6. Ramachandran A, Snehalatha C, Mary S, Mukesh B, Bhaskar AD, Vijay V, Indian Diabetes Prevention Programme (IDPP): The Indian diabetes prevention programme shows that lifestyle modification and metformin prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP-1). Diabetologia 2006; 49:289–297.

7. Li G, Zhang P, Wang J, Gregg EW, Yang W, Gong Q, Li H, Li H, Jiang Y, An Y, Shuai Y, Zhang B, Zhang J, Thompson TJ, Gerzoff RB, Roglic G, Hu Y,Bennett PH: The long-term effect of lifestyle interventions to prevent diabetes in the China Da Qing Diabetes Prevention Study: a 20-year follow-up study. Lancet 2008; 371:1783–1789.

References

8. Metzger BE, Coustan DR: Summary and recommendations of the Fourth International Workshop-Conference on Gestational Diabetes Mellitus: the Organizing Committee. Diabetes Care 21: B161–B167,1998

9. Seshiah V, Balaji V, Balaji MS, Sanjeevi CB, Green A. Gestational diabetes mellitus in India. J Assoc Physicians India 2004; 52: 707-11.

10. Zargar AH, Sheikh MI, Bashir MI, Masoodi SR, Laway BA, Wani AI, et al. Prevalence of gestational diabetes mellitus in Kashmiri women from the Indian Subcontinent. Diabetes Res ClinPract 2004; 66 : 139-45

11. Seshiah V, Balaji V, Balaji MS, Paneerselvam A, Arthi T, Thamizharasi M, et al. Prevalence of gestational diabetes mellitus in South India (Tamil Nadu) - a community based study. J Assoc Physicians India 2008; 56: 329-33.

12. Bryson CL, Ioannou GN, Rulyak SJ, Critchlow C. Association between gestational diabetes and pregnancy-induced hypertension. Am J Epidemiol 2003; 158:1148-53.

13. Mitanchez D. Foetal and neonatal complications in gestational diabetes: perinatal mortality, congenital malformations, macrosomia, shoulder dystocia, birth injuries, neonatal complications. Diabetes Metabol 2010; 36:617-27.

14. Hillier TA, Pedula KL, Schmidt MM, Mullen JA, Charles MA, Pettitt DJ. Childhood obesity and metabolic imprinting: the ongoing effects of maternal hyperglycemia. Diabetes Care 2007; 30:2287-92.

References

15. Clausen TD, Mathiesen ER, Hansen T, Pedersen O, Jensen DM, Lauenborg J, et al. High prevalence of type 2 diabetes and pre-diabetes in adult offspring of women with gestational diabetes mellitus or type 1 diabetes: the role of intrauterine hyperglycemia. Diabetes Care 2008; 31:340-6.

16. Egeland GM, Skjaerven R, Irgens LM. Birth characteristics of women who develop gestational diabetes: population based study. BMJ 2000; 321:546-7.

17. Zhang C, Tobias DK, Chavarro JE, Bao W, Wang D, Ley SH, Hu FB. Adherence to healthy lifestyle and risk of gestational diabetes mellitus: prospective cohort study. BMJ 2014;349:g5450 doi: 10.1136/bmj.g5450

18. Indian Council of Medical Research. Ethical Guidelines for Biomedical Research on Human Participants. NewDelhi, 2006.

19. Mudur G. Indian doctors defend “unethical” anticancer drug trial. BMJ : BMJ. 2001 Aug 11;323(7308):299

20. Solomon CG, Willett WC, Carey VJ, Rich-Edwards J, Hunter DJ, Colditz GA, et al. A prospective study of pregravid determinants of gestational diabetes mellitus. JAMA 1997; 278:1078-83.

21. Tobias DK, Zhang C, Chavarro J, Bowers K, Rich-Edwards J, Rosner B, et al. Pre pregnancy adherence to dietary patterns and lower risk of gestational diabetes mellitus. Am J ClinNutr 2012; 96:289-95.

22. Zhang C, Solomon CG, Manson JE, Hu FB. A prospective study of pregravid physical activity and sedentary behaviors in relation to the risk for gestational diabetes mellitus. Arch Intern Med 2006; 166:543-8.

23. Zhang C, Ning Y. Effect of dietary and lifestyle factors on the risk of gestational diabetes: review of epidemiologic evidence. Am J Clin Nutr 2011; 94:1975S-79S**.**