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The SUGAR-DIP trial: oral medication strategy versus insulin for diabetes in pregnancy, study protocol for a multicenter, open label, non-inferiority, randomized controlled trial

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Complete List of Authors:	de Wit, Leon; University Medical Center Utrecht, Utrecht University, Department of Obstetrics and Gynaecology Rademaker, D.; Amsterdam University Medical Centers, University of Amsterdam, Department of Obstetrics & Gynaecology Voormolen, D.; University Medical Center Utrecht, Utrecht University, Department of Obstetrics & Gynaecology Akerboom, B.; Albert Schweitzer Hospital, Department of Obstetrics & Gynaecology Kiewiet-Kemper, R.; Albert Schweitzer Hospital, Department of Internal Medicine Soeters, M.; Amsterdam University Medical Centers, University of Amsterdam, Department of Endocrinology & Metabolism Verwij-Didden, M.; Bernhoven Hospital, Department of Obstetrics & Gynaecology Assouiki, F.; Bernhoven Hospital, Department of Internal Medicine Schippers, D.; Canisius Wilhelmina Hospital, Department of Obstetrics & Gynaecology Vermeulen, M.; Canisius Wilhelmina Hospital, Department of Internal Medicine Kuppens, S.; Catharina Hospital, Department of Obstetrics & Gynaecology Oosterwerff, M.; Catharina Hospital, Department of Internal Medicine Zwart, J.; Deventer Hospital, Department of Obstetrics & Gynaecology Diekman, M.; Deventer Hospital, Department of Internal Medicine Vogelvang, T.; Diakonessenhuis Utrecht, Department of Obstetrics & Gynaecology Gallas, P.; Diakonessenhuis Utrecht, Department of Internal Medicine Galjaard, S.; Erasmus MC University Medical Center Rotterdam, Department of Obstetrics and Prenatal Medicine Visser, W.; Erasmus MC University Medical Center Rotterdam, Department of Obstetrics and Prenatal Medicine Horree, N.; Flevoziekenhuis, Department of Obstetrics & Gynaecology Klooker, T.; Flevoziekenhuis, Department of Internal Medicine Laan, R.; Gelderse Vallei Hospital, Department of Obstetrics & Gynaecology Heijligenberg, R.; Gelderse Vallei Hospital, Department of Internal Medicine Huisjes, A.; Gelre Hospitals, Department of Obstetrics & Gynaecology

	van Bemmel, T.; Gelre Hospitals, Department of Internal Medicine van Meir, C.; Groene Hart Hospital, Department of Obstetrics & Gynaecology van den Beld, A.; Groene Hart Hospital, Department of Internal Medicine Hermes, W.; Haaglanden Medical Center, Department of Obstetrics & Gynaecology Vidarsdottir, S.; Haaglanden Medical Center, Department of Internal Medicine Veldhuis-Vlug, A.; Medical Center Jan van Goyen, Department of Internal Medicine Dullemond, R.; Jeroen Bosch Hospital, Department of Obstetrics & Gynaecology Jansen, H. J.; Jeroen Bosch Hospital, Department of Internal Medicine Sueters, M.; Leiden University Medical Center, Department of Obstetrics & Gynaecology de Koning, E.; Leiden University Medical Center, Department of Medicine van Laar, J.; Máxima Medical Center, Department of Obstetrics & Gynaecology Wouters-van Poppel, P.; Máxima Medical Center, Department of Internal Medicine Sanson-van Praag, M.; Meander Medical Center, Department of Internal Medicine van den Akker, E.; OLVG, Department of Obstetrics & Gynaecology Brouwer, C.; OLVG, Department of Internal Medicine Hermsen, B.; OLVG, Department of Obstetrics & Gynaecology Potter van Loon, B.; OLVG, Department of Internal Medicine van der Heijden, O.; Radboud University Medical Center Nijmegen, Department of Obstetrics & Gynaecology de Galan, B.; Radboud University Medical Center Nijmegen, Department of Internal Medicine van Leeuwen, M.; Reinier de Graaf Hospital, Department of Obstetrics & Gynaecology Wijbenga, J.; Reinier de Graaf Hospital, Department of Internal Medicine de Boer, K.; Rijnstate Hospital, Department of Obstetrics & Gynaecology van Bon, A.; Rijnstate Hospital, Department of Internal Medicine van der Made, F.; Franciscus Gasthuis & Vlietland, Department of Obstetrics & Gynaecology Eskes, S.; Franciscus Gasthuis & Vlietland, Department of Internal Medicine Zandstra, M.; Spaarne Gasthuis, Department of Obstetrics & Gynaecology van Houtum, W.; Spaarne Gasthuis, Department of Internal Medicine Braams-Lisman, B.; Tergooi, Department of Obstetrics & Gynaecology Daemen-Gubbels, C.; Tergooi, Department of Internal Medicine Wouters, Maurice ; Amsterdam UMC, VU University Medical Center, Department of Obstetrics & Gynaecology IJzerman, R.; Amsterdam UMC, VU University Medical Center, Department of Internal Medicine Mensing van Charante, N.; Dijklander Hospital, Department of Obstetrics & Gynaecology Zwertbroek, R.; Dijklander Hospital, Department of Internal Medicine Bosmans, J; VU University Amsterdam, Department of Health Sciences, Faculty of Science Evers, I.; Meander Medical Center, Department of Obstetrics & Gynaecology Mol, Ben; School of Medicine, Monash University, Melbourne, Australia, Department of Obstetrics and Gynaecology de Valk, H.; University Medical Center Utrecht, Utrecht University, Department of Internal Medicine & Endocrinology Groenendaal , Floris ; University Medical Center Utrecht, Utrecht University, Department of Neonatology

	Naaktgeboren, CA ; University Medical Center Utrecht, Utrecht University, Julius Center for Health Sciences & Primary Care Painter, Rebecca; Amsterdam University Medical Centers, University of Amsterdam, Department of Obstetrics & Gynaecology de Vries, Hans; Amsterdam University Medical Centers, University of Amsterdam, Department of Internal Medicine Franx, Arie; University Medical Center Utrecht, Utrecht University, Department of Obstetrics & Gynaecology van Rijn, Bas; University Medical Center Utrecht, Utrecht University, Department of Obstetrics & Gynaecology; Erasmus MC University Medical Center Rotterdam, Department of Obstetrics & Prenatal Medicine
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The SUGAR-DIP trial: oral medication strategy versus insulin for diabetes in pregnancy, study protocol for a multicenter, open label, non-inferiority, randomized controlled trial

1. L. de Wit, M.D., Department of Obstetrics and Gynaecology, University Medical Center Utrecht, Utrecht University, Lundlaan 6, 3508 AB, Utrecht, the Netherlands. l.dewit-3@umcutrecht.nl

2. D. Rademaker, M.D., Department of Obstetrics and Gynaecology, Amsterdam University Medical Centers, University of Amsterdam, Meibergdreef 9, 1105 AZ, Amsterdam, the Netherlands. d.rademaker@amc.uva.nl

3. D.N. Voormolen, M.D. Ph.D., Department of Obstetrics and Gynaecology, University Medical Center Utrecht, Utrecht University, Lundlaan 6, 3508 AB, Utrecht, the Netherlands. d.p.vanmunster-2@umcutrecht.nl

4. B.M.C. Akerboom, M.D., Department of Obstetrics and Gynaecology, Albert Schweitzer Hospital, Albert Schweitzerplaats 25, 3318 AT, Dordrecht, the Netherlands. b.akerboom@asz.nl

5. R.M. Kiewiet-Kemper, M.D. Ph.D., Department of Internal Medicine, Albert Schweitzer Hospital, Albert Schweitzerplaats 25, 3318 AT, Dordrecht, the Netherlands. r.kiewiet@asz.nl

6. M.R. Soeters, M.D. Ph.D., Department of Endocrinology and Metabolism, Amsterdam University Medical Centers, University of Amsterdam, Meibergdreef 9, 1105 AZ, Amsterdam, the Netherlands. m.r.soeters@amc.uva.nl

7. M.A.L. Verwij-Didden, M.D., Department of Obstetrics and Gynaecology, Bernhoven Hospital, Nistelrodeseweg 10, 5406 PT, Uden, the Netherlands. m.verwij@bernhoven.nl

8. F. Assouiki, M.D., Department of Internal Medicine, Bernhoven Hospital, Nistelrodeseweg 10, 5406 PT, Uden, the Netherlands. f.assouiki@bernhoven.nl

9. D.H. Schippers, M.D., Department of Obstetrics and Gynaecology, Canisius Wilhelmina Hospital, Weg door Jonkerbos 100, 6532 DZ, Nijmegen, the Netherlands. d.schippers@cwz.nl

10. M.A.R. Vermeulen, M.D. Ph.D., Department of Internal Medicine, Canisius Wilhelmina Hospital, Weg door Jonkerbos 100, 6532, DZ, Nijmegen, the Netherlands. mar.vermeulen@cwz.nl

11. S.M.I. Kuppens, M.D. Ph.D., Department of Obstetrics and Gynaecology, Catharina Hospital, Michelangelolaan 2, 5623 EJ, Eindhoven, the Netherlands. simone.kuppens@catharinaziekenhuis.nl

12. M.M. Oosterwerff, M.D. Ph.D., Department of Internal Medicine, Catharina Hospital, Michelangelolaan 2, 5623 EJ, Eindhoven, the Netherlands. mirjam.oosterwerff@catharinaziekenhuis.nl

13. J.J. Zwart, M.D. Ph.D., Department of Obstetrics and Gynaecology, Deventer Hospital, Nico Bolkesteinlaan 75, 7416 SE, Deventer, the Netherlands. j.zwart@dz.nl

14. M.J.M. Diekman, M.D. Ph.D., Department of Internal Medicine, Deventer Hospital, Nico Bolkesteinlaan 75, 7416 SE, Deventer, the Netherlands. m.j.m.diekman@dz.nl

15. T.E. Vogelvang, M.D. Ph.D., Department of Obstetrics and Gynaecology, Diakonessenhuis Utrecht, Bosboomstraat 1, 3582 KE, Utrecht, the Netherlands. tvogelvang@diakhuis.nl

16. P.R.J. Gallas, M.D. Ph.D., Department of Internal Medicine, Diakonessenhuis Utrecht, Bosboomstraat 1, 3582 KE, Utrecht, the Netherlands. rgallas@diakhuis.nl

17. S. Galjaard, M.D. Ph.D., Department of Obstetrics and Prenatal Medicine, Erasmus MC University Medical Center Rotterdam, Doctor Molewaterplein 40, 3015 GD, Rotterdam, the Netherlands. s.galjaard@erasmusmc.nl

18. W. Visser, M.D. Ph.D., Department of Obstetrics and Prenatal Medicine, Erasmus MC University Medical Center Rotterdam, Doctor Molewaterplein 40, 3015 GD, Rotterdam, the Netherlands. willy.visser@erasmusmc.nl

19. N. Horree, M.D. Ph.D., Department of Obstetrics and Gynaecology, Flevoziekenhuis, Hospitaalweg 1, 1315 RA, Almere, the Netherlands. nhorree@flevoziekenhuis.nl

20. T.K. Klooker, M.D. Ph.D., Department of Internal Medicine, Flevoziekenhuis, Hospitaalweg 1, 1315 RA, Almere, the Netherlands. tklooker@flevoziekenhuis.nl

21. R. Laan, M.D., Department of Obstetrics and Gynaecology, Gelderse Vallei Hospital, Willy Brandtlaan 10, 6716 RP, Ede, the Netherlands. laanr@zgv.nl

22. R. Heijligenberg, M.D. Ph.D., Department of Internal Medicine, Gelderse Vallei Hospital, Willy Brandtlaan 10, 7616 RP, Ede, the Netherlands. heijligenbergr@zgv.nl

23. A.J.M. Huisjes, M.D., Department of Obstetrics and Gynaecology, Gelre Hospitals, Albert Schweitzerlaan 31, 7334 DZ, Apeldoorn, the Netherlands. a.huisjes@gelre.nl

24. T. van Bemmel, M.D. Ph.D., Department of Internal Medicine, Gelre Hospitals, Albert Schweitzerlaan 31, 7334 DZ, Apeldoorn, the Netherlands. t.van.bemmel@gelre.nl

25. C.A. van Meir, M.D. Ph.D., Department of Obstetrics and Gynaecology, Groene Hart Hospital, Bleulandweg 10, 2803 HH, Gouda, the Netherlands. claudia.van.meir@ghz.nl

26. A.W. van den Beld, M.D. Ph.D., Department of Internal Medicine, Groene Hart Hospital, Bleulandweg 10, 2803 HH, Gouda, the Netherlands. Annewieke.van.den.beld@ghz.nl

27. W. Hermes, M.D. Ph.D., Department of Obstetrics and Gynaecology, Haaglanden Medical Center, Lijnbaan 32, 2512 VA, the Hague, the Netherlands. w.hermes@haaglandenmc.nl

28. S. Vidarsdottir, M.D. Ph.D., Department of Internal Medicine, Haaglanden Medical Center, Lijnbaan 32, 2512 VA, the Hague, the Netherlands. s.johannssonvidarsdottir@haaglandenmc.nl

29. A.G. Veldhuis-Vlug, M.D. Ph.D., Department of Internal Medicine, Medical Center Jan van Goyen, Jan van Goyenkade 1, 1075 HN, Amsterdam, the Netherlands. aveldhuis@jvg.nl

30. R.C. Dullemond, M.D., Department of Obstetrics and Gynaecology, Jeroen Bosch Hospital, Henri Dunantstraat 1, 5223 GZ, 's-Hertogenbosch, the Netherlands. r.dullemond@jbz.nl

31. H.J. Jansen, M.D. Ph.D., Department of Internal Medicine, Jeroen Bosch Hospital, Henri Dunantstraat 1, 5223 GZ, 's-Hertogenbosch, the Netherlands, h.jansen@jbz.nl

32. M. Sueters, M.D. Ph.D., Department of Obstetrics and Gynaecology, Leiden University Medical Center, Albinusdreef 2, 2333 ZA, Leiden, the Netherlands. m.sueters@lumc.nl

33. E.J.P. de Koning, M.D. Ph.D., Department of Medicine, Leiden University Medical Center, Albinusdreef 2, 2333 ZA, Leiden, the Netherlands. e.dekoning@lumc.nl

34. J.O.E.H. van Laar, M.D. Ph.D., Department of Obstetrics and Gynaecology, Máxima Medical Center, De Run 4600, 5504 DB, Veldhoven, the Netherlands. judith.van.laar@mmc.nl

35. P. Wouters-van Poppel, M.D. Ph.D., Department of Internal Medicine, Máxima Medical Center, De Run 4600, 5504 DB, Veldhoven, the Netherlands. Pleun.van.poppel@mmc.nl

36. M.E. Sanson-van Praag, M.D. Ph.D., Department of Internal Medicine, Meander Medical Center, Maatweg 3, 3813 TZ, Amersfoort, the Netherlands. me.sanson@meandermc.nl

37. E.S. van den Akker, M.D. Ph.D., Department of Obstetrics and Gynaecology, OLVG, Oosterpark 9, 1091 AC, Amsterdam, the Netherlands. e.s.a.vandenakker@olvg.nl

38. C.B. Brouwer, M.D. Ph.D., Department of Internal Medicine, OLVG, Oosterpark 9, 1091 AC, Amsterdam, the Netherlands. c.b.brouwer@olvg.nl

39. B.B. Hermsen, M.D. Ph.D., Department of Obstetrics and Gynaecology, OLVG, Jan Tooropstraat 164, 1061 AE, Amsterdam, the Netherlands. b.hermsen@olvg.nl

40. B.J. Potter van Loon, M.D. Ph.D., Department of Internal Medicine, OLVG, Jan Tooropstraat 164, 1061 AE, Amsterdam, the Netherlands. b.pottervanloon@olvg.nl

41. O.W.H. van der Heijden, M.D. Ph.D., Department of Obstetrics and Gynaecology, Radboud University Medical Center, Geert Grooteplein-Zuid 10, 6525 GA, Nijmegen, the Netherlands. Olivier.vanderheijden@radboudumc.nl

42. B. de Galan, M.D. Ph.D., Department of Internal Medicine, Radboud University Medical Center, Geert Grooteplein-Zuid 10, 6525 GA, Nijmegen, the Netherlands. Bastiaan.degalan@radboudumc.nl

43. M. van Leeuwen, M.D. Ph.D., Department of Obstetrics and Gynaecology, Reinier de Graaf Hospital, Reinier de Graafweg 5, 2625 AD, Delft, the Netherlands. Marsha.vanleeuwen@rdgg.nl

44. J.A. Wijbenga, M.D. Ph.D., Department of Internal Medicine and Gynaecology, Reinier de Graaf Hospital, Reinier de Graafweg 5, 2625 AD, Delft, the Netherlands. A.wijbenga@rdgg.nl

45. K. de Boer, M.D. Ph.D., Department of Obstetrics and Gynaecology, Rijnstate Hospital, Wagnerlaan 55, 6815 AD, Arnhem, the Netherlands. kdeboer@rijnstate.nl

46. A. C. Van Bon, M.D. Ph.D., Department of Internal Medicine, Rijnstate Hospital, Wagnerlaan 55, 6815 AD, Arnhem, the Netherlands. acvanbon@rijnstate.nl

47. F.W. van der Made, M.D., Department of Obstetrics and Gynaecology, Franciscus Gasthuis & Vlietland, Kleiweg 500, 3045 PM, Rotterdam, the Netherlands. f.vandermade@sfg.nl

48. S.A. Eskes, M.D. Ph.D., Department of Internal Medicine, Franciscus Gasthuis & Vlietland, Kleiweg 500, 3045 PM, Rotterdam, the Netherlands. s.eskes@franciscus.nl

49. M. Zandstra, M.D., Department of Obstetrics and Gynaecology, Spaarne Gasthuis, Boerhaavelaan 22, 2035 RC, Haarlem, the Netherlands. mzandstra@spaarnegasthuis.nl

50. W.H. van Houtum, M.D. Ph.D., Department of Internal Medicine, Spaarne Gasthuis, Boerhaavelaan 22, 2035 RC, Haarlem, the Netherlands. wvanhoutum@spaarnegasthuis.nl

51. B.A.M. Braams-Lisman, M.D. Ph.D., Department of Obstetrics and Gynaecology , Tergooi, Rijksstraatweg 1, 1261 AN, Blaricum, the Netherlands. Bbraams-lisman@tergooi.nl

52. C.R.G.M. Daemen-Gubbels, M.D., Department of Internal Medicine, Tergooi, Rijksstraatweg 1, 1261 AN, Blaricum, the Netherlands. cdaemen@tergooi.nl

53. M.G.A.J. Wouters, M.D. Ph.D., Department of Obstetrics and Gynaecology, Amsterdam UMC, VU University Medical Center, de Boelelaan 1117, 1081 HV, Amsterdam, the Netherlands. mgaj.wouters@vumc.nl

54. R.G. IJzerman, M.D. Ph.D., Diabetes Center, Department of Internal Medicine, Amsterdam UMC, VU University Medical Center, de Boelelaan 1117, 1081 HB, Amsterdam, the Netherlands. rg.ijzerman@vumc.nl

55. N.A. Mensing van Charante, M.D., Department of Obstetrics and Gynaecology, Dijklander Hospital, Maelsonstraat 3, 1624 NP, Hoorn, the Netherlands. n.a.mensingvancharante@westfriesgasthuis.nl

56. R. Zwertbroek, M.D., Department of Internal Medicine, Dijklander Hospital, Maelsonstraat 3, 1624 NP, Hoorn, the Netherlands. r.zwertbroek@westfriesgasthuis.nl

57. J.E. Bosmans, Ph.D., Department of Health Sciences, Faculty of Science, Vrije Universiteit Amsterdam, Amsterdam Public Health Research Institute, Amsterdam, the Netherlands. De Boelelaan 1081, 1081 BT Amsterdam, the Netherlands. j.e.bosmans@vu.nl

58. I.M. Evers, M.D. Ph.D., Department of Obstetrics and Gynaecology, Meander Medical Center, Maatweg 3, 3813 TZ, Amersfoort, the Netherlands. im.evers@meandermc.nl

59. B.W.J. Mol, M.D. Ph.D., Department of Obstetrics and Gynaecology, Monash University, Monash Medical Centre 246, Clayton Road Clayton, Victoria 3168, Australia. ben.mol@monash.edu

60. H.W. de Valk, M.D. Ph.D., Department of Internal Medicine and Endocrinology, University Medical Center Utrecht, Utrecht University, Lundlaan 6, 3508 AB, Utrecht, the Netherlands. h.w.devalk@umcutrecht.nl

61. F. Groenendaal, M.D. Ph.D., Department of Neonatology, University Medical Center Utrecht, Utrecht University, Lundlaan 6, 3508 AB, Utrecht, the Netherlands. f.groenendaal@umcutrecht.nl

62. C.A. Naaktgeboren, Ph.D., Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Heidelberglaan 100, 3584 CX, Utrecht, the Netherlands. c.naaktgeboren@umcutrecht.nl

63. R.C. Painter, M.D. Ph.D., Department of Obstetrics and Gynaecology, Amsterdam University Medical Centers, University of Amsterdam, Meibergdreef 9, 1105 AZ, Amsterdam, the Netherlands. r.c.painter@amc.uva.nl

64. J.H. DeVries, M.D. Ph.D., Department of Internal Medicine and Endocrinology, Amsterdam University Medical Centers, University of Amsterdam, Meibergdreef 9, 1105 AZ, Amsterdam, the Netherlands. j.h.devries@amc.uva.nl

65. A. Franx, M.D., Ph.D., Department of Obstetrics and Gynaecology, University Medical Center Utrecht, Utrecht University, Lundlaan 6, 3508 AB, Utrecht, the Netherlands. a.franx-2@umcutrecht.nl

66. B.B. van Rijn, M.D. Ph.D., Department of Obstetrics and Gynaecology, University Medical Center Utrecht, Utrecht University, Lundlaan 6, 3508 AB, Utrecht, the Netherlands. Department of Obstetrics and Prenatal Medicine, Erasmus MC University Medical Center Rotterdam, Doctor Molewaterplein 40, 3015 GD, Rotterdam, the Netherlands. b.vanrijn@erasmusmc.nl

Corresponding author
B.B. van Rijn, M.D., Ph.D.
Department of Obstetrics & Prenatal Medicine
Erasmus MC University Medical Center Rotterdam
Doctor Molewaterplein 40
3015 GD, Rotterdam, the Netherlands
b.vanrijn@erasmusmc.nl

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ABSTRACT

Introduction: In women with gestational diabetes mellitus (GDM) requiring pharmacotherapy, insulin was the established first-line treatment. More recently oral glucose lowering drugs (OGLDs) have gained popularity as a patient-friendly, less expensive, and safe alternative. Monotherapy with metformin or glibenclamide (glyburide) is incorporated in several international guidelines. In women who do not reach sufficient glucose control with OGLD monotherapy, usually insulin is added, either with or without continuation of OGLDs. No reliable data from clinical trials, however, is available on the effectiveness of a treatment strategy using all three agents: metformin, glibenclamide, and insulin, in a stepwise approach, compared with insulin-only therapy for improving pregnancy outcomes. In this trial we aim to assess the clinical effectiveness, cost-effectiveness and patient experience of a stepwise combined OGLD treatment protocol, compared to conventional insulin-based therapy for GDM.

Methods: The SUGAR-DIP trial is an open label, multicenter randomized controlled non-inferiority trial. Participants are women with GDM who do not reach target glycemic control with modification of diet, between 16-34 weeks of gestation. Participants will be randomized to either treatment with OGLDs, starting with metformin and supplemented as needed with glibenclamide, or randomized to treatment with insulin. In women who do not reach target glycemic control with combined metformin and glibenclamide, glibenclamide will be substituted with insulin, while continuing metformin. The primary outcome will be the incidence of large-for-gestational-age infants (birth weight >90th percentile). Secondary outcome measures are maternal diabetes-related endpoints, obstetric complications, neonatal complications and cost-effectiveness analysis. Outcomes will be analyzed according to the intention-to-treat principle.

Ethics and dissemination: The study protocol was approved by the Ethics Committee of the Utrecht University Medical Center. Approval by the boards of management for all participating hospitals will be obtained. Trial results will be submitted for publication in peer-reviewed journals.

Trial registration: Netherlands Trial Registry NTR6134 (November 2016).

Keywords: gestational diabetes mellitus, oral glucose lowering drugs, antihyperglycemic agents, antidiabetic medication, metformin, glyburide, glibenclamide, insulin, randomized controlled trial, large-for-gestational-age.

Article summary:

Strengths and limitations of this study

- This is the first open-label randomized controlled trial that directly compares a step-wise treatment protocol using a combination of oral glucose lowering drugs (OGLDs) to insulin as a first-line treatment for GDM not responding to diet
- The randomized multi-center design minimizes the risk of bias and increases generalizability of the results
- Variation in diagnostic thresholds and treatment targets for GDM may need to be addressed to assess the value of this strategy across different populations

INTRODUCTION:

The prevalence of gestational diabetes mellitus (GDM) is rising and currently affects approximately 5-10% of all pregnancies.[1,2] GDM carries significant perinatal risks for pregnancy and childbirth, such as large-for-gestational-age infants, stillbirth, shoulder dystocia, obstructed labor, preeclampsia and neonatal hypoglycemia.[3–6] In addition, increasing concern exists about the impact of GDM on offspring development and associated long-term risks for obesity and chronic disease in children born to mothers with GDM.[7,8]

The rising number of women diagnosed with GDM requiring treatment is increasingly putting pressure on health care resources. Effective treatment for GDM treatment requires a multidisciplinary approach by endocrinologists, obstetricians and diabetes nurse specialists. Current treatment of GDM focuses on achieving optimal glycemic control. When blood glucose levels, usually based on self-monitoring, fall outside the target range despite lifestyle- and dietary advice, treatment with antihyperglycemic medication is indicated.[9,10] As pharmacologic treatment subcutaneous insulin injections have traditionally been used as first-choice treatment for GDM and is still advocated in many, but not all, guidelines.[11–13] In recent years, clinical research and experience with oral glucose lowering drugs (OGLDs) has shown promising results as a treatment alternative that may substitute insulin in many women.[14,15]

Metformin and glibenclamide (glyburide) are the OGLDs most studied for diabetes in pregnancy. Both are already widely used in the treatment of GDM and accepted as a safe first-line pharmacological treatment option in several guidelines.[16–19] A 2014 retrospective cohort study from the United States showed that the use of glibenclamide had increased from 7.4% in 2000 to 64.5% in 2011, becoming the most common treatment for GDM requiring pharmacotherapy in 2007.[17] In the United Kingdom, incorporated in the NICE guidelines (National Institute for Health and Care Excellence, UK), metformin is the first choice treatment, supplemented with insulin if needed.[20] Insulin is offered to women if metformin is contraindicated or unacceptable to the patient, or target glucose values are not met with

metformin only. The NICE guidelines state that glibenclamide could be considered an option for women in whom blood glucose targets are not achieved with metformin, but decline insulin therapy, or for those who cannot tolerate metformin. A recent statement by the Society of Maternal-Fetal Medicine (SMFM) Committee further endorses OGLDs as a reasonable and safe first-line pharmacologic treatment in GDM.[21] In contrast, in the Netherlands, insulin has remained the drug of choice in the majority of hospitals.

Two 2017 Cochrane Reviews on 11 and 53 studies (1487, and 7381 women) concluded that due to insufficient high-quality evidence no single agent is superior in the treatment of GDM.[22,23] And although the use of OGLDs is widespread, there is an ongoing discussion on which drug should be first line treatment after lifestyle- and dietary interventions.[24] Both insulin and oral agents have advantages and disadvantages. Insulin is safe and effective, however is considered burdensome by pregnant women, requires intensive glucose monitoring, and is associated with episodes of maternal hypoglycemia.[25] OGLDs are less costly, less burdensome and associated with higher patient satisfaction.[15,18,26–28] Metformin has the advantage over insulin that hypoglycemic events do not occur, but it is less potent when compared to glibenclamide, can cause gastro-intestinal side-effects and is possibly associated with more spontaneous preterm deliveries.[16] Glibenclamide, similar to insulin, is more potent in its glucose-lowering effect and may cause hypoglycemia in the mother and newborn.[14,29] And although intrauterine exposure to metformin or glibenclamide is not associated with congenital anomalies, much less is known about direct fetal metabolic effects and long-term effects on mothers and offspring.[30]

With current OGLD monotherapy, consisting of either metformin or glibenclamide, in women who do not reach glycemic control, prompting the need for additional measures, in general OGLDs are replaced by or supplemented with insulin. A combination of oral agents may be an interesting strategy for GDM treatment, however current evidence is insufficient to determine the optimal use of OGLDs. In a recent randomized controlled trial by Nachum *et al.* in 104 women with GDM, powered for glycemic control, combination therapy of metformin and

glibenclamide decreased the need for additional insulin from 32% to 11% (p = 0.0002) compared to monotherapy.[31] Metformin as the first-line therapy combined with glibenclamide if needed was associated with the highest treatment success. These data support the need for a well-powered large scale randomized controlled trial to compare a step-wise approach combining metformin and glibenclamide to conventional insulin therapy to study effects on pregnancy outcomes.

In the SUGAR-DIP trial, a multicenter randomized controlled trial, we aim to assess non-inferiority of treatment with metformin, and in case of insufficient glycemic control the addition of glibenclamide, compared to immediate insulin in the treatment of GDM. We expect that a proportion of patients will achieve glycemic control with metformin only. By adding glibenclamide in combined treatment with metformin, we expect to achieve glycemic control as good as by insulin, while maintaining the benefits and ease of a less burdensome treatment with oral medication. We will assess the clinical effectiveness, cost-effectiveness and patient experience of stepwise oral antihyperglycemic medication to treat GDM compared to conventional insulin-based treatment strategy.

METHODS:

Design and setting:

The SUGAR-DIP trial is a multicenter non-inferiority randomized controlled trial (RCT). The study will be open label as oral drugs and insulin cannot be administered individually in a blinded way. The study will be conducted within the setting of the Dutch Consortium for Healthcare Evaluation and Research in Obstetrics and Gynaecology – NVOG Consortium 2.0,[32] a collaborative network of all major hospitals in the Netherlands and the Dutch Society of Obstetrics and Gynaecology (NVOG) and performed by treatment teams generally consisting of an internist, a gynaecologist and diabetes nurses. In the preparation of the trial, the patient organisation Dutch Diabetes Association (Diabetes Vereniging Nederland) was involved and provided valuable input, representing the patient perspective in the study protocol. The trial was

approved by the Medical Research Ethics Committee (MREC) of the UMC Utrecht. Trial reference number: 16-523/M. The trial is registered in the Netherlands Trial Registry on 29 November 2016 under the number NTR6134.[33]

Participants and eligibility criteria:

Women diagnosed with GDM who have not reached target glycemic control with dietary and lifestyle adaptations and thus meet the criteria for additional treatment with antihyperglycemic medication between 16 to 34 weeks of gestation, will be eligible for inclusion. Target glycemic control is defined by the NVOG(Dutch College O&G) diabetes in pregnancy guideline as fasting glucose concentration ≤5.3 mmol/L, 1-hour postprandial ≤7.8 mmol/L or 2-hour postprandial ≤6.7 mmol/L.[34]

The diagnosis of GDM is made according to Dutch national guidelines, using a 75-gram oral glucose tolerance test.[34] Due to a transition in diagnostic thresholds, both the WHO 1999 (fasting ≥7.0 mmol/L or 2-hour postload ≥7.8 mmol/L) and WHO 2013 criteria (fasting ≥5.1 mmol/L, 1-hour postload ≥10.0 or 2-hour postload ≥8.5 mmol/L) for venous plasma glucose values were used to diagnose GDM. Screening in the Netherlands is conducted according to a high risk strategy, and takes place in the second trimester (24-28 weeks) among pregnant women with one or more of the following risk factors are present: a history of GDM, BMI>30 (kg/m^2), a history of a neonate with a birth weight >95th percentile or >4500 grams, a first degree family member with diabetes, polycystic ovary syndrome, a history of an unexplained intra-uterine death or an ethnicity with higher diabetes risk (e.g. women from South-Asia, Indian descent / Surinamese, Afro-Caribbean, Middle-Eastern, Moroccan or Egyptian ethnicity). In case of a history of GDM in a previous pregnancy an OGTT as early as 16 weeks of gestation is recommended, to be repeated at 24-28 weeks if normal. An OGTT may also be performed in cased of suspected fetal macrosomia, polyhydramnios, or symptoms of polydipsia or polyuria.

Additional inclusion criteria for the SUGAR-DIP trial are: (1) maternal age ≥18 years (2) singleton pregnancy (3) ability to understand the Dutch or English language and (4) ability to provide

written informed consent. Patients who meet any of the following criteria are excluded from the study: (1) known pre-existing type 1 or type 2 diabetes mellitus (2) severe medical or psychiatric comorbidities (3) significant liver disease or renal insufficiency, or any other known condition with contraindications for the use of either metformin or glibenclamide (4) pregnancy with a fetus affected by major congenital birth defects and/or chromosomal abnormality.

Recruitment and randomisation:

Eligible women will be informed and invited to participate by either their diabetes care or obstetric care provider, i.e. physician, obstetrician, midwife, or diabetes nurse. Following counselling, written informed consent is obtained and participants are individually randomized to either stepwise OGLDs or insulin. Randomization is performed through a central web-based tool (Castor EDC, Ciwit B.V., the Netherlands and Castor Research Inc, USA), using a 1:1 ratio and block randomization with a variable block size of 4 and 6.

Intervention and control:

Figure I. displays the stepwise treatment strategy for the intervention (OLGD) and control (insulin) group.

Oral glucose lowering drugs (OGLDs):

In women allocated to the OGLD strategy, metformin is initiated with a starting dose of 500 mg once daily for 3 days, followed by an increase of 500 mg every 3 days to the final daily dose of 2000 mg divided into 2 doses. In case of serious side effects (e.g. severe nausea, persistent vomiting or diarrhoea), the metformin dose can be lowered to the maximum dose tolerated with acceptable side effects. Participants are advised to take metformin during or shortly after a meal to reduce side effects. In case of insufficient glycemic control with metformin at the maximum (tolerated) dose, glibenclamide will be added at a starting dose of 2.5 mg once daily. Glibenclamide can be increased if glycemic goals are not met with increments of 2.5 mg every week, up to a maximum dose of 15 mg daily. In case of insufficient glycemic control with both

metformin and glibenclamide at the maximum doses, glibenclamide will be discontinued and replaced by insulin, while metformin will be continued.

Insulin:

Participants randomized to insulin treatment will receive insulin according to usual practice, i.e. in incremental doses until glycemic targets are met.[35] This includes both short- and long-acting insulin.

Study procedures:

Diabetes care:

In all participants, a specialized diabetes nurse or internal medicine specialist will review glycemic control every 1-2 weeks using the following target values for glucose, as measured by capillary glucose self-testing: fasting $\leq$ 5.3 mmol/L, 1 hour postprandial $\leq$ 7.8 mmol/L and 2 hours postprandial $\leq$ 6.7 mmol/L. If titration of medication requires more frequent feedback, participants will be given the option to contact their diabetes treatment specialist in between scheduled visits. All participants receive the usual instructions regarding hypoglycemic events (glucose <4.0 mmol/L). A participant diary is used to document glucose values and medication use, and is reviewed at every visit. Frequency of self-monitoring will be discussed on an individual basis with the treating diabetes team. Weight is documented at study inclusion and at every subsequent visit. Blood sampling for glycated haemoglobin (HbA1c) is performed at study inclusion, at 30 weeks and at 36 weeks of pregnancy.

Obstetric care:

All participants will receive obstetrical care based on usual practice for gestational diabetes mellitus requiring pharmacological therapy. This includes assessment of fetal biometry at weeks 26-28, 30-32 and 34-36 of pregnancy by measuring fetal abdominal circumference (AC), femur length (FL), head circumference (HC), estimated fetal weight (EFW) (Hadlock or similar) and amniotic fluid volume. The timing of delivery follows local protocol, based on national

guidelines.[34] Induction of labour around 38-39 weeks of gestation is generally recommended for women with GDM requiring medication. Both oral antihyperglycemic agents and insulin may be discontinued on the day of delivery in case of induced labor or as soon as labor is established after spontaneous onset. Monitoring of glucose levels during labor is advised.

Neonatal care:

Neonatal glucose monitoring will be performed serially for up to 12-24 hours after delivery in accordance to local protocol in participating sites. We defined neonatal hypoglycemia as a plasma glucose concentration <2.6 mmol/L and severe neonatal hypoglycemia as <2.0 mmol/L.[36] Time and plasma glucose values are documented as well as any NICU admission and interventions used to regulate neonatal glucoses.

Postpartum:

Participants will attend routine obstetric and diabetes care provider appointments around 5-6 weeks postpartum at which time glucose self-monitoring will be carried out to detect persistent postpartum hyperglycemia.

Outcome measures

Primary outcome measure:

The primary outcome is a large-for-gestational-age (LGA) infant. Large-for-gestational-age is defined as a birth weight $\geq 90^{th}$ percentile, using the Dutch Perinatal Registry (PRN) reference charts.[37]

Secondary outcome measures

Secondary outcomes include maternal hypoglycemia (biochemical hypoglycemia <3.9 mmol/L, symptomatic hypoglycemia, severe hypoglycemia prompting the need for help by another person and/or hospital admission for hypoglycemia), elective- and emergency Caesarean section, pregnancy related hypertensive disorders including Pregnancy Induced Hypertension (PIH) and preeclampsia (PE), preterm delivery (delivery <37 weeks of gestation), postpartum

neonatal hypoglycemia (moderate: serum glucose <2.6 mmol/L, severe: serum glucose <2.0 mmol/L), neonatal hyperbilirubinemia requiring phototherapy, neonatal Medium Care or Intensive Care admission and a cost-effectiveness analysis.

Furthermore, a number of maternal baseline characteristics, obstetric- and neonatal outcomes, diabetes-related endpoints, biomarkers and laboratory examinations will be assessed *(see supplement 1 and 2)*.

Follow-up

Details regarding outcomes, including maternal and neonatal hospital admissions or complications are recorded up to 6 weeks postpartum. Long-term follow-up of mother and child is not part of the initial trial, however participants will be informed about planned long-term follow-up and asked to provide additional personal information and contact details on the patient information and informed consent form at study inclusion.

Patient perspective and treatment satisfaction:

A custom made side-effects form will be used to monitor side effects, the actions taken because of side effects and to what extent participants were affected by the side effects. Treatment satisfaction is also measured around 36 weeks of pregnancy using the Diabetes Treatment Satisfaction Questionnaire (DTSQ), consisting of 8 questions regarding diabetes treatment and patient experience.[38,39] Two additional questions regarding side-effects and discomfort were provided by the copyright holder from a related treatment satisfaction measures for another condition, and added as items 9 and 10 of the DTSQ, to be analysed separately.[40]

Safety and monitoring:

An independent Data and Safety Monitoring Board (DSMB) will be established to safeguard the interests of trial participants, assess the safety and efficacy of the interventions during the trial period and monitor the overall conduct of the clinical trial. An interim safety review is planned at 300 included participants and will be carried out by an independent statistician.

All serious adverse events (SAE) reported by the subject or observed by the investigator or staff will be recorded. SAE definitions and standards for expedited reporting follow the ICH GCP guidelines on safety reporting.[41] All SAEs will be reported to the accredited ethics committee that approved the protocol, according to the requirements of that committee.

Sample size:

The primary outcome measure, rate of LGA infants, is anticipated to occur in 20% of patients in both study groups, based on a Dutch study cohort.[42] We have set the non-inferiority limit at 8%, which is equivalent to excluding a relative risk in the OGLD treatment compared with conventional insulin-based therapy greater than 1.4. With a one-sided significance level (α) of 0.025 and a power of 0.8, the sample size is calculated at 393 patients in each arm. Accounting for a loss to follow-up of 3%, 810 patients are needed (405 per arm).

Analyses and reporting of results:

Primary and secondary outcomes:

Primary analysis of the RCT results will be according to the intention-to-treat principle. Missing data will be handled according to the complete-case analysis principle, based on the availability of the components needed to determine the primary endpoint. Results will be reported according to CONSORT guidelines, using the extension for non-inferiority trials. In case of substantial cross-over (>5%), a per protocol analysis is used additionally to the intention-to-treat analysis. Cross-over is defined as patients not receiving the treatment allocated by randomization (e.g. participant never started treatment, treatment is no longer necessary for instance due to improved dietary adaptations, side-effects, or stopping treatment shortly after randomization).

For the primary analysis, the non-inferiority of metformin/glibenclamide versus insulin for preventing large-for-gestational-age infants will be established when the upper bounds of the two-sided 95% confidence interval for the risk ratio is less than 1.4. Large-for-gestational-age will be defined as birth weight >90th percentile.[37] Results for the primary outcome will also be

presented as absolute and relative risks (along with 95% confidence intervals (CI)) and numbers needed to treat (if applicable). Analyses will not be adjusted for any observed differences in baseline characteristics between the arms.

The secondary outcome measures will be analysed similar to the primary outcome measure. Categorical secondary outcomes will be assessed by comparing the event rates in the two groups using a chi-square test with a p-value of 0.05 and also by presenting absolute and relative risks. For continuous secondary outcomes, differences between groups will be assessed with the student's t-test if the outcome is normally distributed and with a non-parametric Mann-Whitney U test if skewed. These outcomes will be presented per group as means with standard deviation, geometric means with 95% CI, or as median with interquartile range, depending on distribution.

Subgroup analyses:

Subgroup analyses will be performed for women with and without a history of GDM, a family history of diabetes mellitus (first and/or second degree relative), BMI (normal weight, overweight, obese), according to severity of GDM (fasting and 2 hour OGTT glucose value by various diagnostic criteria and cut-offs), sex (neonate). Additionally, potential causes for treatment failure of metformin alone will also be explored. Within the patients receiving oral agents, the outcome rate will be compared between the patients whose blood glucose could be regulated by metformin alone and those patients who also required glibenclamide and even additional insulin. Patient characteristics between these groups will be compared to identify possible contributing factors to metformin treatment failure.

Economic evaluation:

An economic evaluation will be conducted alongside the randomized controlled trial according to guidelines issued by the National Health Care Institute.[43] The EuroQuol questionnaire (EQ-5D-5L) for health status measures is used at time of study inclusion, 36 weeks of pregnancy and 4-6 weeks postpartum.[44] Further Health Technology Assessment questionnaires are based on

the iMTA PCQ (Productivity Cost Questionnaire) and MCQ (Medical Consumption Questionnaire), issued at 36 weeks of pregnancy and 4-6 weeks postpartum.[45,46] The statistical analysis for the economic evaluation will be done according to the intention-to-treat principle. Missing data will be imputed using multiple imputation. If OGLDs are non-inferior to insulin as hypothesized, a cost minimization analysis will be performed to investigate which intervention is associated with lower costs. If non-inferiority cannot be shown, a cost-effectiveness analysis will be performed. The costs will be analyzed from both a societal (i.e. healthcare costs, patient and family costs, and costs in other sectors) and healthcare perspective (i.e. only healthcare costs). In the cost minimization analysis the differences in costs between OGLDs and insulin will be evaluated using linear multilevel regression models with adjustment for covariates and effect modifiers if necessary. Bootstrapping with stratification for center will be done to estimate 95% confidence intervals around differences in costs. In the cost-effectiveness analysis cost and effect differences will be estimated using seemingly unrelated regression analyses while adjusting for confounders and effect modifiers if necessary. Incremental cost-effectiveness ratios (ICERs) will be calculated by dividing the difference in mean total costs between the treatment groups by the difference in mean effects. Bootstrapping with stratification for center will be used to estimate uncertainty surrounding the ICERs. Uncertainty surrounding the ICERs will be graphically presented on cost-effectiveness planes. Cost-effectiveness acceptability curves showing the probability that the intervention is cost-effective in comparison with usual care for a range of different ceiling ratios will also be estimated.[47] A sensitivity analysis will be performed to investigate the robustness of the results to variation in the most influential cost parameters such as medication and time required for clinical consults.

Data handling:

Baseline data including patient demographics, obstetric and medical history, details regarding the pregnancy, delivery outcomes and diabetes treatment will be recorded using a web-based electronic case record form (eCRF) using Castor EDC. The full eCRF is provided as a supplemental file (*Supplement 2*). A study monitor will periodically visit participating centres, assessing quality of data and auditing trial conduct. Patient privacy will be ensured by allocation

of unique participant numbers, which will be used on all study documentation. The participant code is only available to the local investigator and research staff.

Ethics and dissemination

This trial has been approved by the Medical Research Ethics Committee (MREC) of the UMC Utrecht. Trial reference number: 16-523/G-M-X. The MREC of the UMC Utrecht is accredited by the Central Committee on Research Involving Human Subjects (CCMO) since November 1999. For all participating hospitals and study sites approval by the boards of management will be obtained. The CCMO has issued a 'No grounds for non-acceptance' for the SUGAR-DIP trial. Research with a medicinal product must undergo an extra, marginal review alongside the review by the reviewing party (MREC). The competent authority (CCMO) checks if there are 'motivated objections' against the study. For this the European adverse reactions database (EudraVigilance) is checked for any previously reported suspected adverse reactions to the medicinal product, which could lead to unacceptable risks to the participating research subject. Furthermore, the CCMO is responsible as the competent authority for entering data into the European EudraCT database. EudraCT number for this trial: 2016-001401-16.

Changes to the study protocol are documented in amendments. Amendments are submitted for approval to the MREC. Major changes will be updated on the trial registration website.[33] The full study protocol, including amendments, is publically available on the study website.[48]

After completion of the trial the principal investigator will report on the results of the main study and submit a manuscript to a peer-reviewed medical journal. Supplementary analyses will be reported separately.

Author contributions:

Study concept, trial design and study protocol: LW, DNV, JEB, IME, BWM, HWV, FG, CAN, RCP, JHD, AF, BBR

Acquisition of data: LW, DR, BMCA, RMKK, RCP, MRS, MALVD, FA, DHS, MARV, SMIK, MMO, JJZ, MJMD, TEV, PRJG, SG, WV, NH, TKK, RL, RH, AJMH, TB, CAM, AWB, WH, SV, AGVV, RCD, HJJ, MS, EJPK, JOEHL, PWP, IME, MESP, ESA, CBB, BBH, BJP, OWHH, BG, ML, JAW, KB, ACB, FWM, SAE, MZ, WHH, BAMBL, CRGMDG, MGAJW, RGIJ, NAMC, RZ

Analysis and interpretation of data: LW, DR, DNV, JEB, IME, BWM, HWV, FG, CAN, RCP, JHD, AF, BBR

Drafting of the manuscript: LW, DR, CAN, RCP, JHD, AF, BBR

Critical revision of the manuscript for important intellectual content: LW, DR, DNV, JEB, IME, BWM, HWV, FG, CAN, RCP, JHD, AF, BBR, BMCA, RMKK, MRS, MALVD, FA, DHS, MARV, SMIK, MMO, JJZ, MJMD, TEV, PRJG, SG, WV, NH, TKK, RL, RH, AJMH, TB, CAM, AWB, WH, SV, AGVV, RCD, HJJ, MS, EJPK, JOEHL, PWP, MESP, ESA, CBB, BBH, BJP, OWHH, BG, ML, JAW, KB, ACB, FWM, SAE, MZ, WHH, BAMBL, CRGMDG, MGAJW, RGIJ, NAMC, RZ
Study supervision: JHD, AF, BBR

Trial Sponsor:
Institution: University Medical Center Utrecht, Wilhelmina Children's Hospital
Principal investigator: Prof. Dr. A. Franx
Address: Lundlaan 6, 3584 EA, Utrecht, the Netherlands

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Competing interests:
JHD sits on advisory boards for Novo Nordisk A/S
BWM is supported by a NHMRC Practitioner Fellowship (GNT1082548)
BWM reports consultancy for ObsEva, Merck KGaA and Guerbet

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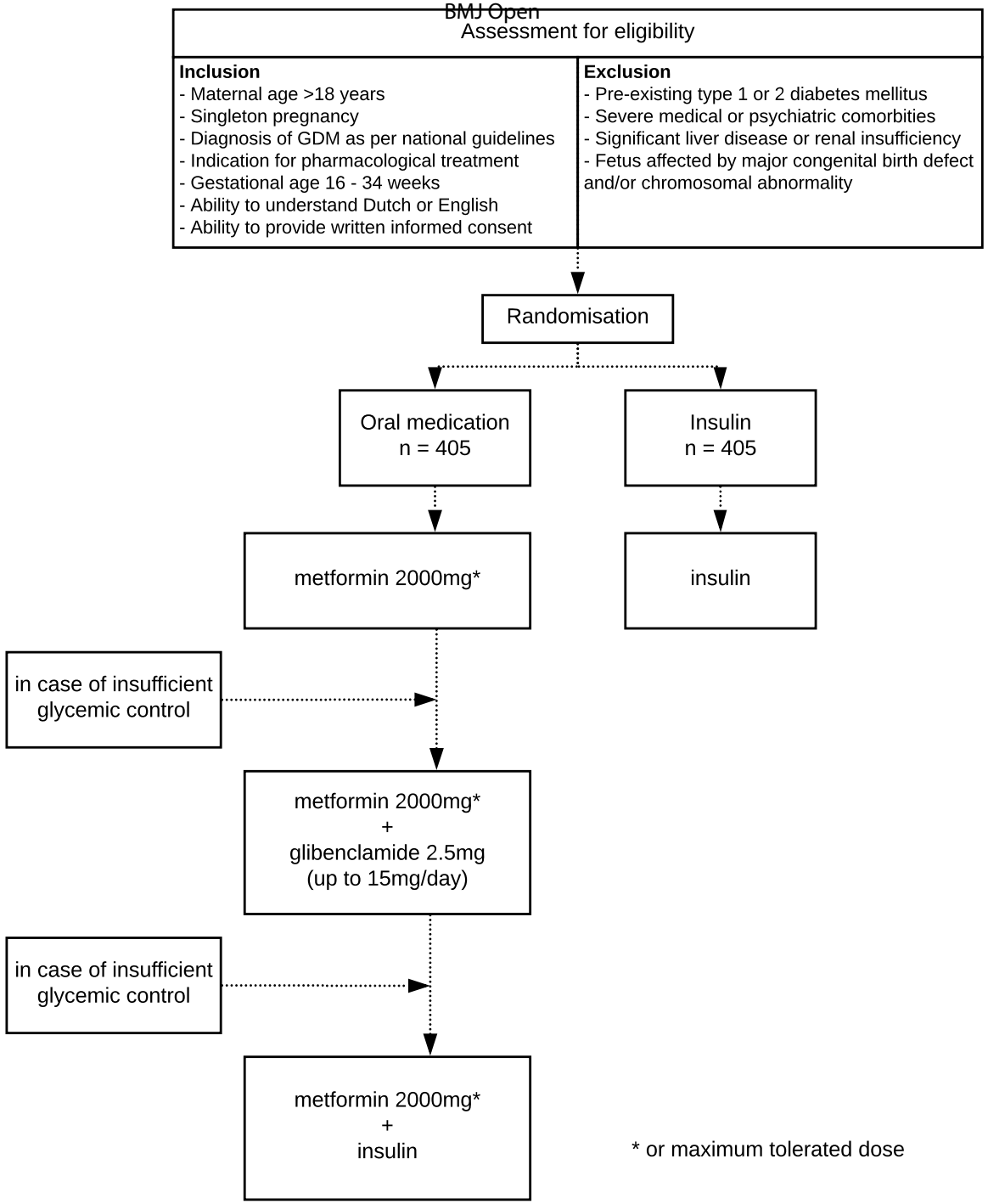
FIGURE HEADINGS:

FIGURE 1:

Figure I: flowchart of comparator (oral glucose lowering drugs) versus control (insulin)



Supplemental file 1: SUGAR-DIP additional study parameters and endpoints

Maternal baseline characteristics

- BMI at study entrance
- Age (y)
- Parity
- Mean arterial blood pressure at study entry (mmHg)
- Intoxications (smoking, alcohol use)
- Ethnicity: Caucasian, Indian/Pakistani/Bangladesi, Afro-Caribbean (Antilles, Surinam-creole), Hindu/Caribbean (Surinam Hindu), African (Sub-Sahara), Middle Eastern/North African (Turkish, Moroccan), Asian, Other
- PCOS; polycystic ovarian syndrome
- Thyroid problems: hypo- or hyperthyroidism
- History of gestational diabetes mellitus
- History of psychological problems
- Family history: diabetes mellitus, gestational diabetes, hypertension, preeclampsia, congenital defects
- Conception: spontaneous, fertility treatment (clomifene citrate, gonadotropins, IVF, ICSI)
- Reason for GDM screening
- Blood glucose measures of OGTT (fasting, post load)
- Gestational age at time of OGTT

Neonatal characteristics

- Gestational age at delivery
- Birth weight (g)
- Weight at discharge (g)
- Sex
- Apgar score 5 – 10 minutes
- Umbilical artery pH levels
- Respiratory support > 24 hours
- Culture proven sepsis
- Neonatal blood glucose levels 1-3-6-12 (24) hours after delivery
- Intravenous glucose therapy
- Convulsions
- Intrauterine fetal death
- Neonatal death
- Congenital defect/anomaly

Obstetric / delivery characteristics

- Ultrasound examinations: fetal biometry (abdominal circumference, femur length, head circumference, estimated fetal weight) amniotic fluid, fetal heart and brain (where available)
- Induction of labour
- Birth injury: shoulder dystocia (a delivery that requires additional obstetric maneuvers following failure of gentle downward traction on the fetal head to effect delivery of the shoulders), clavicle/humerus fracture or Erb's palsy
- Vacuum assisted delivery
- Blood loss (ml)
- Post-partum haemorrhage >1L
- Blood transfusion
- Sphincter rupture

Diabetes related endpoints

- Ketoacidosis
- Fasting and postprandial blood glucose levels (study diary)
- Maternal HbA1c (study inclusion, 30 weeks and 36 weeks of gestation)
- Maternal weight gain >12kg
- Final daily dose of insulin (study diary)
- Final daily dose of metformin/glibenclamide (study diary)
- Time to reach glycemic control (study diary)
- Treatment failure: percentage of patients requiring insulin after metformin and glibenclamide
- Side effects: metformin, glibenclamide, insulin

Biomarkers and laboratory measurements

- Cord-blood: C-peptide, glucose, insulin, triglycerides (where available)
- Cord-blood: metformin / glibenclamide levels (where available)
- Placenta: pathological examination (where available)

Biobanking (where available)

- Maternal serum
- Placental biopsies
- Umbilical cord blood
- Umbilical cord tissue

SUGAR-DIP trial

Oral medication strategy versus insulin for diabetes in pregnancy

Electronic case report form

CRF data entry and randomization:

www.castoredc.com

- ○ Single possible answer
- □ Multiple answers possible

General information	
Maternal age at time of randomization	(years)
Estimated date of delivery	(dd-mm-yyyy)
In-exclusion	
Age 18 years or older	○ Yes ○ No
Singleton pregnancy	○ Yes ○ No
Diagnosis if gestational diabetes mellitus as per national guidelines	○ Yes ○ No
Indication for pharmacological treatment of GDM	○ Yes ○ No
Gestational age between 16 and 34 weeks	○ Yes ○ No
Ability to understand Dutch or English	○ Yes ○ No
Known pre-existent type I or II diabetes mellitus	○ Yes ○ No
Severe medical or psychological comorbidity	○ Yes ○ No
Liver disease or kidney failure, or any other condition with contraindications for the use of either metformin or glibenclamide	○ Yes ○ No
Fetus with major congenital birth defect and/or chromosomal abnormality	○ Yes ○ No
Informed consent & Randomization	
Patient has provided written informed consent	○ Yes ○ No
Date of informed consent	(dd-mm-yyyy)
Date of randomization	(dd-mm-yyyy)
Gestational age at time of randomization	….. weeks + ….. days
Medical history	
Ethnicity	○ Caucasian/white ○ Indian/Pakistani/Bangladesi/Hindu ○ Black/African (Sub-Sahara) ○ Middle Eastern + North African (Turkey, Morocco, Egypt) ○ Asian ○ Other ○ Unknown
Diagnosis of Polycystic Ovary Syndrome (PCOS)	○ Yes ○ No
Thyroid problems: hypo- or hyperthyroidism	○ Hypothyroidism ○ Hyperthyroidism

	○ Thyroid problem, but type is unknown ○ No ○ Unknown
History of psychological problems	☐ Depression ☐ Anxiety disorder ☐ Burn-out ☐ Other ☐ None ☐ Unknown
Maternal chronic or pre-existent hypertension	○ Yes (requiring medication) ○ Yes (not requiring medication) ○ No ○ Unknown
Maternal medication use (other than folic acid and vitamins) during pregnancy	☐ No ☐ Aspirin (Acetylsalicylic acid) ☐ Levothyroxine / Thyrax ☐ SSRI (including sertraline, (es)citalopram, paroxetine, fluoxetine) ☐ Tricyclic antidepressant (including amitryptiline, nortryptiline) ☐ Other ☐ Unknown
Family history	
Family history of type I / type II diabetes mellitus (1st or 2nd degree)	○ Yes ○ No ○ Unknown
Family history of gestational diabetes mellitus (1st or 2nd degree)	○ Yes ○ No ○ Unknown
Family history if hypertension (1st or 2nd degree)	○ Yes ○ No ○ Unknown
Family history of preeclampsia (1st or 2nd degree)	○ Yes ○ No ○ Unknown
Family history of congenital defects (1st or 2nd degree)	○ Yes ○ No ○ Unknown
Obstetric history	
Gravidity	(n)
Parity	(n)
Living children	(n)
Miscarriage – spontaneous abortion	(n)
Abortus provocatus – induced abortion	(n)
Extra-uterine gravidity	(n)
Intra-uterine death > 16 weeks	(n)
Any previous pregnancy with gestational diabetes mellitus?	○ No (no GDM in previous pregnancies) ○ Yes ○ Unknown

How many pregnancies with gestational diabetes mellitus?	(n)
Any pregnancy with GDM treated with insulin?	○ No ○ Yes ○ Unknown
Any previous pregnancy with pregnancy induced hypertension (PIH)?	○ No (no PIH in previous pregnancies) ○ Yes ○ Unknown
Any previous pregnancy with preeclampsia (PE)?	○ No (no PE in previous pregnancies) ○ Yes ○ Unknown
Any previous pregnancy with Hemolysis Elevated Liver enzymes and Low Platelets syndrome (HELLP)?	○ No (no HELLP in previous pregnancies) ○ Yes ○ Unknown
Any previous pregnancy with a preterm delivery (< 37 weeks of gestation)	○ No (no preterm delivery in previous pregnancies) ○ Yes ○ Unknown
A caesarean section (primary or secondary) in the past?	○ No (no caesarean section in the past) ○ Yes ○ Unknown
Any hemorrhagia postpartum (HPP, blood loss ≥ 1000ml) in the past?	○ No (no HPP in the past) ○ Yes ○ Unknown
Please complete the following questions for all previous pregnancies > 16 weeks	Parity number: …… Gestational age: ….. weeks + ….. days Gender: male, female, unknown Birth weight (grams): …..
Current pregnancy	
Mode of conception	○ Spontaneous ○ Clomifene ovulation induction ○ Intra-uterine insemination (IUI) ○ IVF / ICSI ○ Egg cell donation ○ Unknown
Maternal height	(cm)
Maternal weight at start of pregnancy	(kg)
Maternal weight at time of study inclusion	(kg)
Maternal weight at time of delivery / last pre-delivery visit	(kg)
Maternal weight gain (total) >12kg	○ Yes ○ No ○ Unknown
Maternal blood pressure systolic at first antenatal visit	(mmHg)
Maternal blood pressure diastolic at first antenatal visit	(mmHg)
Smoking during pregnancy	○ No

	○ Quit in first trimester ○ Quit later in pregnancy ○ Yes (still smoking) ○ Unknown
Alcohol use during pregnancy	○ Yes ○ No ○ Unknown
Glucose value (random) in first trimester	(mmol/L)
Diagnostic test used to determine gestational diabetes	○ Oral glucose tolerance test (75 gram) ○ Oral glucose tolerance test (100 gram) ○ Fasting glucose level ○ Glucose day curve ○ Other
Date of GDM diagnosis	(dd-mm-yyyy)
Glucose value of 75 gram OGTT fasting (laboratory)	(mmol/L)
Glucose value of 75 gram OGTT 2 hours (laboratory)	(mmol/L)
Glucose value of 100 gram OGTT fasting (laboratory)	(mmol/L)
Glucose value of 100 gram OGTT 2 hours (laboratory)	(mmol/L)
Glucose value of 100 gram OGTT 3 hours (laboratory)	(mmol/L)
Glucose value fasting (laboratory)	(mmol/L)
Highest glucose value of glucose day curve	(mmol/L)
Main reason to perform OGTT	○ Suspected macrosomia/estimated fetal weight >p90 (current pregnancy) ○ Family history with diabetes ○ Obesity ○ Prior pregnancy with GDM ○ Ethnicity ○ Other ○ Unknown
Pregnancy complications	
Pregnancy induced hypertension (systolic BP > 140mmHg or diastolic BP > 90mmHg)	○ Yes ○ No ○ Unknown
Pregnancy induced hypertension	○ Without medication ○ With medication (for instance labetolol or methyldopa) ○ Unknown whether medication was used ○ Other
Preeclampsia (hypertension with albuminuria)	○ Yes ○ No ○ Unknown
HELLP	○ Yes ○ No

	○ Unknown
Trombo-embolic complications (deep venous thrombosis or lung-embolus)	○ Yes ○ No ○ Unknown
Hospital admission because of severe glycemic dysregulation	○ Yes ○ No ○ Unknown
Fetal structural defects (ultrasound)	○ Yes ○ No ○ Unknown
Fetal structural defects (ultrasound)	☐ Central nervous system, including spina bifida and anencephaly ☐ Skeletal system, including caudal regression syndrome, limb defects and sacral agenesis ☐ Cardiovascular, including transposition of the great vessels, septal defects, single umbilical artery (SUA), coarctation of the aorta ☐ Gastrointestinal, including duodenal atresia ☐ Unknown which system ☐ Other
Macrosomia (EFW >p90 or FAC >p90 or mentioned in conclusion)	○ Yes ○ No ○ Unknown
Intra-uterine growth restriction (IUGR) (EFW <p10 or FAC <p10 or mentioned in conclusion)	○ Yes ○ No ○ Unknown
Polyhydramnios (ultrasound)	○ Yes ○ No ○ Unknown
Oligohydramnios (ultrasound)	○ Yes ○ No ○ Unknown
Corticosteroid used? (for instance because of imminent premature birth)	○ Yes ○ No ○ Unknown
Intra-uterine death	○ Yes ○ No
Date of intra-uterine death	(dd-mm-yyyy)
Delivery	
Date of last dose of antidiabetic medication	(dd-mm-yyyy)
Time of last dose of antidiabetic medication	(hh-mm)
Onset of labour	○ Spontaneously ○ Primary caesarean section ○ Induction
Was induction planned for a different reason than gestational diabetes mellitus?	○ Yes ○ No

	○ Unknown
Reason for induction	☐ Elective ☐ Ruptured membranes ☐ Hypertension ☐ Preeclampsia ☐ HELLP syndrome ☐ Maternal: blood glucose dysregulation ☐ Maternal: other → specify ☐ Fetal: suspected macrosomia ☐ Fetal: suspected intra-uterine growth restriction ☐ Fetal: no movements ☐ Fetal: heart rate anomaly ☐ Fetal: oligohydramnios ☐ Fetal: meconium ☐ Fetal: other → specify ☐ Other → specify
Method of induction	☐ Foley catheter / mechanical ☐ Prostaglandins ☐ Amniotomy ☐ Oxytocin ☐ Other ☐ Unknown
Indication for primary caesarean section	☐ Elective: breech ☐ Elective: obstetric history (previous caesarean section) ☐ Elective: obstetric history (total sphincter rupture) ☐ Elective: obstetric history (other) ☐ Fetal distress ☐ Fetal: intra-uterine growth restriction ☐ Fetal: other ☐ Maternal: hypertension ☐ Maternal: preeclampsia ☐ Maternal: HELLP syndrome ☐ Maternal: other ☐ Unknown
Pain relief during delivery	☐ None ☐ Opioid subcutaneous (pethidine) ☐ Opioid intravenous (remifentanil) ☐ Nitrous oxide ☐ Epidural ☐ Other ☐ Unknown
Medication during labour	☐ Oxytocin ☐ Antibiotics ☐ Tocolytics ☐ Glucose/insulin intravenous ☐ Antihypertensive agents intravenous ☐ Other → specify

	☐ None ☐ Unknown
Fever during delivery	○ No ○ Yes (>38°C <38.5°C) ○ Yes (≥38.5°C) ○ Unknown
Fetal presentation	○ Cephalic ○ Breech ○ Other
Route of delivery	○ Vaginal, spontaneously ○ Instrumental (vacuum extraction) ○ Instrumental (forcipal extraction) ○ Secondary caesarean section
Indication for vacuum / forcipal extraction	○ Fetal distress ○ Failure to progress ○ Maternal indication ○ Other fetal indication ○ Unknown
Indication for secondary caesarean section	○ Fetal distress ○ Failure to progress ○ Failed induction ○ Maternal indication ○ Failed vacuum / forcipal extraction ○ Other fetal indication ○ Unknown
Were maneuvers used because of shoulder dystocia?	☐ No (no shoulder dystocia) ☐ Traction to the fetal head ☐ McRoberts ☐ Rubin ☐ All-fours ☐ Manual delivery of posterior arm ☐ Intentional breaking of clavicle ☐ Shoulder dystocia but unknown which maneuvers were used ☐ Other
Amniotic fluid	○ Clear ○ Meconium stained ○ Unknown
Delivery of the placenta	○ Spontaneously / controlled cord traction ○ Manual removal in operating room ○ Removed during caesarean section ○ Unknown
Total blood loss	(ml)
Blood transfusion	○ Yes ○ No ○ Unknown
Perineum	☐ No laceration(s) ☐ First / second degree laceration(s)

	☐ Third degree laceration(s) ☐ Episiotomy ☐ Unknown
Neonatal data	
Date of birth	(dd-mm-yyyy)
Gestational age at birth	….. weeks + ….. days
Live birth	○ Yes ○ No
Neonatal death	○ No ○ Yes (intra-uterine death) ○ Yes, <24 hours postpartum ○ Yes, >24 hours postpartum
Gender	○ Female ○ Male ○ Unknown
Apgar score 1 minute postpartum	
Apgar score 5 minutes postpartum	
Apgar score 10 minutes postpartum	
Umbilical cord blood pH (arterial)	
Umbilical cord blood base excess (arterial)	
Umbilical cord blood pH (venous)	
Umbilical cord blood base excess (venous)	
Birth weight	(grams)
Fracture	☐ None ☐ Humerus ☐ Clavicle ☐ Other ☐ Unknown
Erbs palsy	○ No ○ Yes ○ Unknown
Preterm birth (<37 weeks of gestation)	○ No ○ Yes (iatrogenic) ○ Yes (spontaneous)
Neonatal congenital malformation: heart	○ No ○ Yes ○ Unknown
Neonatal congenital malformation: neural tube	○ No ○ Yes ○ Unknown
Neonatal congenital malformation: urogenital	○ No ○ Yes ○ Unknown
Neonatal congenital malformation: other	○ No ○ Yes ○ Unknown
First neonatal glucose postpartum	(mmol/L)
Date of first neonatal glucose testing postpartum	(dd-mm-yyyy)
Time of first neonatal glucose testing postpartum	(hh:mm)

Second neonatal glucose value postpartum	(mmol/L)
Date of second neonatal glucose testing postpartum	(dd-mm-yyyy)
Time of second neonatal glucose testing postpartum	(hh:mm)
Third neonatal glucose value postpartum	(mmol/L)
Date of third neonatal glucose testing postpartum	(dd-mm-yyyy)
Time of third neonatal glucose testing postpartum	(hh:mm)
Fourth neonatal glucose value postpartum	(mmol/L)
Date of fourth neonatal glucose testing postpartum	(dd-mm-yyyy)
Time of fourth neonatal glucose testing postpartum	(hh:mm)
Fifth neonatal glucose value postpartum	(mmol/L)
Date of fifth neonatal glucose testing postpartum	(dd-mm-yyyy)
Time of fifth neonatal glucose testing postpartum	(hh:mm)
Sixth neonatal glucose value postpartum	(mmol/L)
Date of sixth neonatal glucose testing postpartum	(dd-mm-yyyy)
Time of sixth neonatal glucose testing postpartum	(hh:mm)
Any neonatal glucose value between 2.0-2.6mmol/L (≥2.0 <2.7) during in hospital admission?	○ No ○ Yes, one value between 2.0 and 2.6 ○ Yes, more than one value between 2.0 and 2.6 ○ Unknown
Any neonatal glucose value <2.0mmol/L during hospital admission?	○ No ○ Yes, one value <2.0 ○ Yes, more than one value <2.0 ○ Unknown
Postpartum	
Were mother or child admitted directly postpartum? (including postpartum observation of mother/child)	○ No (mother and child went home directly after delivery ○ Yes, maternal admission only ○ Yes, maternal and neonatal admission ○ Yes, neonatal admission only
Maternal: what was the reason for admission?	☐ Maternal observation/routine stay (for instance because of more blood loss than usual or post-caesarean) ☐ Neonatal observation (for instance because of blood glucose evaluation) ☐ Fluxus (HPP) ☐ Pregnancy induced hypertension ☐ Preeclampsia ☐ HELLP syndrome ☐ Glycemic dysregulation ☐ Thrombo-embolic event

	☐ Hemodynamically unstable (Intensive Care) ☐ Infection ☐ Other
Maternal: type of admission	○ Ward ○ Medium Care ○ Intensive Care
Maternal: discharge to	○ Home ○ Other ward ○ Medium Care ○ Intensive Care ○ Other hospital
Maternal: date of transfer	(dd-mm-yyyy)
Maternal: type of admission after transfer	○ Ward ○ Medium Care ○ Intensive Care
Maternal: date of final discharge to home	(dd-mm-yyyy)
Neonatal: what was the reason for admission?	☐ Routine observation for blood glucoses ☐ Routine observation for meconium ☐ Routine observation for suspected infection ☐ Hypoglycemia without i.v. glucose ☐ Hypoglycemia with iv glucose ☐ Hyperbilirubinemia with phototherapy ☐ Hyperbilirubinemia without phototherapy ☐ Respiratory distress syndrome (RDS) / respiratory support or oxygen >24 hours ☐ Broncho pulmonal dysplasia (BPD) ☐ Intraventricular haemorrhage ☐ Sepsis ☐ Necrotizing enterocolitis ☐ Convulsions ☐ Partial exchange transfusion ☐ Trombocyte transfusion ☐ Prematurity ☐ Asphyxia ☐ Other
Neonatal: type of admission	○ Ward ○ Medium Care ○ Intensive Care
Neonatal: discharge to	○ Home ○ Ward ○ Medium Care ○ Intensive Care
Neonatal: date of transfer	(dd-mm-yyyy)
Neonatal: type of admission after transfer	○ Ward ○ Medium Care

	○ Intensive Care
Neonatal: date of final discharge to home	(dd-mm-yyyy)
Neonatal weight at time of discharge	(grams)
Did the neonate receive iv glucose infusion postpartum?	○ Yes ○ No ○ Unknown
How many days of iv glucose infusion?	(days)
Diabetes treatment	
What treatment was the participant randomized to?	○ Insulin ○ Oral hypoglycemic agents
Did the participant ever use: metformin	○ Yes ○ No ○ Unknown
On which date did the participant start with metformin?	(dd-mm-yyyy)
On which date did the participant stop with metformin?	(dd-mm-yyyy)
Did the participant ever use: glibenclamide	○ Yes ○ No ○ Unknown
On which date did the participant start with glibenclamide?	(dd-mm-yyyy)
On which date did the participant stop with glibenclamide?	(dd-mm-yyyy)
Did the participant ever use: insulin?	○ Yes ○ No ○ Unknown
On which date did the participant start with insulin? (If multiple types of insulin were used, use the start date of the first type of insulin)	(dd-mm-yyyy)
On which date did the participant stop with insulin? (If multiple types of insulin were used, use the start date of the first type of insulin)	(dd-mm-yyyy)
Glucose profile most recent before or at randomization: fasting value	(mmol/L)
Glucose profile most recent before or at randomization: after breakfast value	(mmol/L)
Glucose profile most recent before or at randomization: after lunch value	(mmol/L)
Glucose profile most recent before or at randomization: after dinner value	(mmol/L)
Most recent HbA1c value before or at randomization	(mmol/mol)
Date of most recent HbA1c value before or at randomization	(dd-mm-yyyy)
HbA1c value at 30-31 weeks of gestation	(mmol/mol)
Date of HbA1c value at 30-31 weeks of gestation	(dd-mm-yyyy)

HbA1c value at 35-36 weeks of gestation	(mmol/mol)
Date of HbA1c value at 35-36 weeks of gestation	(dd-mm-yyyy)
Additional tests	
Umbilical cord blood C-peptide value	(pmol/L)
Umbilical cord blood glucose value	(mmol/L)
Umbilical cord blood insulin value	(mIU/L)
Umbilical cord blood fructosamine value	(µmol/L)
Umbilical cord blood triglycerides	(mmol/L)
End of study	
Was there a protocol violation?	○ No ○ Yes ○ Unknown
Did a Serious Adverse Event (SAE) occur during the study until 6 weeks postpartum? (If yes, please report the SAE to the sponsor)	○ No ○ Yes ○ Unknown
Did a Suspected Unexpected Serious Adverse Reaction (SUSAR) occur during the study until 6 weeks postpartum? (If yes, please report the SUSAR to the sponsor)	○ No ○ Yes ○ Unknown
Please specify if the subject completed the entire course of the study as specified in the study protocol or discontinued the study:	○ Completed ○ Discontinued
If discontinued, please specify the most appropriate reason for early termination	○ Subject violates one or more of the inclusion/exclusion criteria ○ Adverse event ○ Participant deceased ○ Participant lost to follow up ○ Participant withdrew consent to use personal data ○ Investigator's and/or physician's decision ○ Total study is early terminated ○ Other reason
Has the participant signed informed consent for follow-up?	○ Yes ○ No
Has the participant provided contact information to allow follow-up?	○ Yes ○ No

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Page numbers displayed at each item concern the pages in the protocol manuscript
For applicable items which are not incorporated in the protocol manuscript, we reference to the publically available study protocol document.

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	7 + 13
	2b	All items from the World Health Organization Trial Registration Data Set	Included in registry
Protocol version	3	Date and version identifier	Trial website
Funding	4	Sources and types of financial, material, and other support	22
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1-6 and 21-22
	5b	Name and contact information for the trial sponsor	22
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	NA, investigator initiated

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Publically available study protocol
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	10-12
	6b	Explanation for choice of comparators	10-12
Objectives	7	Specific objectives or hypotheses	12
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	12
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	12
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	13-14
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	14-15
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	14-15
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	15
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	15-16

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	16-17
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	15-17
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	18
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	14

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	14
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	NA
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	14
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	11
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	29-41
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Publically available study protocol
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Publically available study protocol
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	18-19
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	19
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	18
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Publically available study protocol
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	17
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	17
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	20
Ethics and dissemination			

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	20
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	20
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	13
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Publically available study protocol
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	19-20
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	21
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Publically available study protocol
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Publically available study protocol
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	20
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	20
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	20, study website

Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA_____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.

BMJ Open

The SUGAR-DIP trial: oral medication strategy versus insulin for diabetes in pregnancy, study protocol for a multicenter, open label, non-inferiority, randomized controlled trial

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Complete List of Authors:	de Wit, Leon; University Medical Center Utrecht, Utrecht University, Department of Obstetrics and Gynaecology Rademaker, D.; Amsterdam University Medical Centers, University of Amsterdam, Department of Obstetrics & Gynaecology Voormolen, D.; University Medical Center Utrecht, Utrecht University, Department of Obstetrics & Gynaecology Akerboom, B.; Albert Schweitzer Hospital, Department of Obstetrics & Gynaecology Kiewiet-Kemper, R.; Albert Schweitzer Hospital, Department of Internal Medicine Soeters, M.; Amsterdam University Medical Centers, University of Amsterdam, Department of Endocrinology & Metabolism Verwij-Didden, M.; Bernhoven Hospital, Department of Obstetrics & Gynaecology Assouiki, F.; Bernhoven Hospital, Department of Internal Medicine Schippers, D.; Canisius Wilhelmina Hospital, Department of Obstetrics & Gynaecology Vermeulen, M.; Canisius Wilhelmina Hospital, Department of Internal Medicine Kuppens, S.; Catharina Hospital, Department of Obstetrics & Gynaecology Oosterwerff, M.; Catharina Hospital, Department of Internal Medicine Zwart, J.; Deventer Hospital, Department of Obstetrics & Gynaecology Diekman, M.; Deventer Hospital, Department of Internal Medicine Vogelvang, T.; Diakonessenhuis Utrecht, Department of Obstetrics & Gynaecology Gallas, P.; Diakonessenhuis Utrecht, Department of Internal Medicine Galjaard, S.; Erasmus MC University Medical Center Rotterdam, Department of Obstetrics and Prenatal Medicine Visser, W.; Erasmus MC University Medical Center Rotterdam, Department of Obstetrics and Prenatal Medicine Horree, N.; Flevoziekenhuis, Department of Obstetrics & Gynaecology Klooker, T.; Flevoziekenhuis, Department of Internal Medicine Laan, R.; Gelderse Vallei Hospital, Department of Obstetrics & Gynaecology Heijligenberg, R.; Gelderse Vallei Hospital, Department of Internal Medicine Huisjes, A.; Gelre Hospitals, Department of Obstetrics & Gynaecology

	van Bemmel, T.; Gelre Hospitals, Department of Internal Medicine van Meir, C.; Groene Hart Hospital, Department of Obstetrics & Gynaecology van den Beld, A.; Groene Hart Hospital, Department of Internal Medicine Hermes, W.; Haaglanden Medical Center, Department of Obstetrics & Gynaecology Vidarsdottir, S.; Haaglanden Medical Center, Department of Internal Medicine Veldhuis-Vlug, A.; Medical Center Jan van Goyen, Department of Internal Medicine Dullemond, R.; Jeroen Bosch Hospital, Department of Obstetrics & Gynaecology Jansen, H. J.; Jeroen Bosch Hospital, Department of Internal Medicine Sueters, M.; Leiden University Medical Center, Department of Obstetrics & Gynaecology de Koning, E.; Leiden University Medical Center, Department of Medicine van Laar, J.; Máxima Medical Center, Department of Obstetrics & Gynaecology Wouters-van Poppel, P.; Máxima Medical Center, Department of Internal Medicine Sanson-van Praag, M.; Meander Medical Center, Department of Internal Medicine van den Akker, E.; OLVG, Department of Obstetrics & Gynaecology Brouwer, C.; OLVG, Department of Internal Medicine Hermsen, B.; OLVG, Department of Obstetrics & Gynaecology Potter van Loon, B.; OLVG, Department of Internal Medicine van der Heijden, O.; Radboud University Medical Center Nijmegen, Department of Obstetrics & Gynaecology de Galan, B.; Radboud University Medical Center Nijmegen, Department of Internal Medicine van Leeuwen, M.; Reinier de Graaf Hospital, Department of Obstetrics & Gynaecology Wijbenga, J.; Reinier de Graaf Hospital, Department of Internal Medicine de Boer, K.; Rijnstate Hospital, Department of Obstetrics & Gynaecology van Bon, A.; Rijnstate Hospital, Department of Internal Medicine van der Made, F.; Franciscus Gasthuis & Vlietland, Department of Obstetrics & Gynaecology Eskes, S.; Franciscus Gasthuis & Vlietland, Department of Internal Medicine Zandstra, M.; Spaarne Gasthuis, Department of Obstetrics & Gynaecology van Houtum, W.; Spaarne Gasthuis, Department of Internal Medicine Braams-Lisman, B.; Tergooi, Department of Obstetrics & Gynaecology Daemen-Gubbels, C.; Tergooi, Department of Internal Medicine Wouters, Maurice ; Amsterdam UMC, VU University Medical Center, Department of Obstetrics & Gynaecology IJzerman, R.; Amsterdam UMC, VU University Medical Center, Department of Internal Medicine Mensing van Charante, N.; Dijklander Hospital, Department of Obstetrics & Gynaecology Zwertbroek, R.; Dijklander Hospital, Department of Internal Medicine Bosmans, J; VU University Amsterdam, Department of Health Sciences, Faculty of Science Evers, I.; Meander Medical Center, Department of Obstetrics & Gynaecology Mol, Ben; School of Medicine, Monash University, Melbourne, Australia, Department of Obstetrics and Gynaecology de Valk, H.; University Medical Center Utrecht, Utrecht University, Department of Internal Medicine & Endocrinology Groenendaal , Floris ; University Medical Center Utrecht, Utrecht University, Department of Neonatology

	Naaktgeboren, CA ; University Medical Center Utrecht, Utrecht University, Julius Center for Health Sciences & Primary Care Painter, Rebecca; Amsterdam University Medical Centers, University of Amsterdam, Department of Obstetrics & Gynaecology de Vries, Hans; Amsterdam University Medical Centers, University of Amsterdam, Department of Internal Medicine Franx, Arie; University Medical Center Utrecht, Utrecht University, Department of Obstetrics & Gynaecology van Rijn, Bas; University Medical Center Utrecht, Utrecht University, Department of Obstetrics & Gynaecology; Erasmus MC University Medical Center Rotterdam, Department of Obstetrics & Prenatal Medicine
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The SUGAR-DIP trial: oral medication strategy versus insulin for diabetes in pregnancy, study protocol for a multicenter, open label, non-inferiority, randomized controlled trial

1. L. de Wit, M.D., Department of Obstetrics and Gynaecology, University Medical Center Utrecht, Utrecht University, Lundlaan 6, 3508 AB, Utrecht, the Netherlands. l.dewit-3@umcutrecht.nl

2. D. Rademaker, M.D., Department of Obstetrics and Gynaecology, Amsterdam University Medical Centers, University of Amsterdam, Meibergdreef 9, 1105 AZ, Amsterdam, the Netherlands. d.rademaker@amc.uva.nl

3. D.N. Voormolen, M.D. Ph.D., Department of Obstetrics and Gynaecology, University Medical Center Utrecht, Utrecht University, Lundlaan 6, 3508 AB, Utrecht, the Netherlands. d.p.vanmunster-2@umcutrecht.nl

4. B.M.C. Akerboom, M.D., Department of Obstetrics and Gynaecology, Albert Schweitzer Hospital, Albert Schweitzerplaats 25, 3318 AT, Dordrecht, the Netherlands. b.akerboom@asz.nl

5. R.M. Kiewiet-Kemper, M.D. Ph.D., Department of Internal Medicine, Albert Schweitzer Hospital, Albert Schweitzerplaats 25, 3318 AT, Dordrecht, the Netherlands. r.kiewiet@asz.nl

6. M.R. Soeters, M.D. Ph.D., Department of Endocrinology and Metabolism, Amsterdam University Medical Centers, University of Amsterdam, Meibergdreef 9, 1105 AZ, Amsterdam, the Netherlands. m.r.soeters@amc.uva.nl

7. M.A.L. Verwij-Didden, M.D., Department of Obstetrics and Gynaecology, Bernhoven Hospital, Nistelrodeseweg 10, 5406 PT, Uden, the Netherlands. m.verwij@bernhoven.nl

8. F. Assouiki, M.D., Department of Internal Medicine, Bernhoven Hospital, Nistelrodeseweg 10, 5406 PT, Uden, the Netherlands. f.assouiki@bernhoven.nl

9. D.H. Schippers, M.D., Department of Obstetrics and Gynaecology, Canisius Wilhelmina Hospital, Weg door Jonkerbos 100, 6532 DZ, Nijmegen, the Netherlands. d.schippers@cwz.nl

10. M.A.R. Vermeulen, M.D. Ph.D., Department of Internal Medicine, Canisius Wilhelmina Hospital, Weg door Jonkerbos 100, 6532, DZ, Nijmegen, the Netherlands. mar.vermeulen@cwz.nl

11. S.M.I. Kuppens, M.D. Ph.D., Department of Obstetrics and Gynaecology, Catharina Hospital, Michelangelolaan 2, 5623 EJ, Eindhoven, the Netherlands. simone.kuppens@catharinaziekenhuis.nl

12. M.M. Oosterwerff, M.D. Ph.D., Department of Internal Medicine, Catharina Hospital, Michelangelolaan 2, 5623 EJ, Eindhoven, the Netherlands. mirjam.oosterwerff@catharinaziekenhuis.nl

13. J.J. Zwart, M.D. Ph.D., Department of Obstetrics and Gynaecology, Deventer Hospital, Nico Bolkesteinlaan 75, 7416 SE, Deventer, the Netherlands. j.zwart@dz.nl

14. M.J.M. Diekman, M.D. Ph.D., Department of Internal Medicine, Deventer Hospital, Nico Bolkesteinlaan 75, 7416 SE, Deventer, the Netherlands. m.j.m.diekman@dz.nl

15. T.E. Vogelvang, M.D. Ph.D., Department of Obstetrics and Gynaecology, Diakonessenhuis Utrecht, Bosboomstraat 1, 3582 KE, Utrecht, the Netherlands. tvogelvang@diakhuis.nl

16. P.R.J. Gallas, M.D. Ph.D., Department of Internal Medicine, Diakonessenhuis Utrecht, Bosboomstraat 1, 3582 KE, Utrecht, the Netherlands. rgallas@diakhuis.nl

17. S. Galjaard, M.D. Ph.D., Department of Obstetrics and Prenatal Medicine, Erasmus MC University Medical Center Rotterdam, Doctor Molewaterplein 40, 3015 GD, Rotterdam, the Netherlands. s.galjaard@erasmusmc.nl

18. W. Visser, M.D. Ph.D., Department of Obstetrics and Prenatal Medicine, Erasmus MC University Medical Center Rotterdam, Doctor Molewaterplein 40, 3015 GD, Rotterdam, the Netherlands. willy.visser@erasmusmc.nl

19. N. Horree, M.D. Ph.D., Department of Obstetrics and Gynaecology, Flevoziekenhuis, Hospitaalweg 1, 1315 RA, Almere, the Netherlands. nhorree@flevoziekenhuis.nl

20. T.K. Klooker, M.D. Ph.D., Department of Internal Medicine, Flevoziekenhuis, Hospitaalweg 1, 1315 RA, Almere, the Netherlands. tklooker@flevoziekenhuis.nl

21. R. Laan, M.D., Department of Obstetrics and Gynaecology, Gelderse Vallei Hospital, Willy Brandtlaan 10, 6716 RP, Ede, the Netherlands. laanr@zgv.nl

22. R. Heijligenberg, M.D. Ph.D., Department of Internal Medicine, Gelderse Vallei Hospital, Willy Brandtlaan 10, 7616 RP, Ede, the Netherlands. heijligenbergr@zgv.nl

23. A.J.M. Huisjes, M.D., Department of Obstetrics and Gynaecology, Gelre Hospitals, Albert Schweitzerlaan 31, 7334 DZ, Apeldoorn, the Netherlands. a.huisjes@gelre.nl

24. T. van Bemmel, M.D. Ph.D., Department of Internal Medicine, Gelre Hospitals, Albert Schweitzerlaan 31, 7334 DZ, Apeldoorn, the Netherlands. t.van.bemmel@gelre.nl

25. C.A. van Meir, M.D. Ph.D., Department of Obstetrics and Gynaecology, Groene Hart Hospital, Bleulandweg 10, 2803 HH, Gouda, the Netherlands. claudia.van.meir@ghz.nl

26. A.W. van den Beld, M.D. Ph.D., Department of Internal Medicine, Groene Hart Hospital, Bleulandweg 10, 2803 HH, Gouda, the Netherlands. Annewieke.van.den.beld@ghz.nl

27. W. Hermes, M.D. Ph.D., Department of Obstetrics and Gynaecology, Haaglanden Medical Center, Lijnbaan 32, 2512 VA, the Hague, the Netherlands. w.hermes@haaglandenmc.nl

28. S. Vidarsdottir, M.D. Ph.D., Department of Internal Medicine, Haaglanden Medical Center, Lijnbaan 32, 2512 VA, the Hague, the Netherlands. s.johannssonvidarsdottir@haaglandenmc.nl

29. A.G. Veldhuis-Vlug, M.D. Ph.D., Department of Internal Medicine, Medical Center Jan van Goyen, Jan van Goyenkade 1, 1075 HN, Amsterdam, the Netherlands. aveldhuis@jvg.nl

30. R.C. Dullemond, M.D., Department of Obstetrics and Gynaecology, Jeroen Bosch Hospital, Henri Dunantstraat 1, 5223 GZ, 's-Hertogenbosch, the Netherlands. r.dullemond@jbz.nl

31. H.J. Jansen, M.D. Ph.D., Department of Internal Medicine, Jeroen Bosch Hospital, Henri Dunantstraat 1, 5223 GZ, 's-Hertogenbosch, the Netherlands, h.jansen@jbz.nl

32. M. Sueters, M.D. Ph.D., Department of Obstetrics and Gynaecology, Leiden University Medical Center, Albinusdreef 2, 2333 ZA, Leiden, the Netherlands. m.sueters@lumc.nl

33. E.J.P. de Koning, M.D. Ph.D., Department of Medicine, Leiden University Medical Center, Albinusdreef 2, 2333 ZA, Leiden, the Netherlands. e.dekoning@lumc.nl

34. J.O.E.H. van Laar, M.D. Ph.D., Department of Obstetrics and Gynaecology, Máxima Medical Center, De Run 4600, 5504 DB, Veldhoven, the Netherlands. judith.van.laar@mmc.nl

35. P. Wouters-van Poppel, M.D. Ph.D., Department of Internal Medicine, Máxima Medical Center, De Run 4600, 5504 DB, Veldhoven, the Netherlands. Pleun.van.poppel@mmc.nl

36. M.E. Sanson-van Praag, M.D. Ph.D., Department of Internal Medicine, Meander Medical Center, Maatweg 3, 3813 TZ, Amersfoort, the Netherlands. me.sanson@meandermc.nl

37. E.S. van den Akker, M.D. Ph.D., Department of Obstetrics and Gynaecology, OLVG, Oosterpark 9, 1091 AC, Amsterdam, the Netherlands. e.s.a.vandenakker@olvg.nl

38. C.B. Brouwer, M.D. Ph.D., Department of Internal Medicine, OLVG, Oosterpark 9, 1091 AC, Amsterdam, the Netherlands. c.b.brouwer@olvg.nl

39. B.B. Hermsen, M.D. Ph.D., Department of Obstetrics and Gynaecology, OLVG, Jan Tooropstraat 164, 1061 AE, Amsterdam, the Netherlands. b.hermsen@olvg.nl

40. B.J. Potter van Loon, M.D. Ph.D., Department of Internal Medicine, OLVG, Jan Tooropstraat 164, 1061 AE, Amsterdam, the Netherlands. b.pottervanloon@olvg.nl

41. O.W.H. van der Heijden, M.D. Ph.D., Department of Obstetrics and Gynaecology, Radboud University Medical Center, Geert Grooteplein-Zuid 10, 6525 GA, Nijmegen, the Netherlands. Olivier.vanderheijden@radboudumc.nl

42. B. de Galan, M.D. Ph.D., Department of Internal Medicine, Radboud University Medical Center, Geert Grooteplein-Zuid 10, 6525 GA, Nijmegen, the Netherlands. Bastiaan.degalan@radboudumc.nl

43. M. van Leeuwen, M.D. Ph.D., Department of Obstetrics and Gynaecology, Reinier de Graaf Hospital, Reinier de Graafweg 5, 2625 AD, Delft, the Netherlands. Marsha.vanleeuwen@rdgg.nl

44. J.A. Wijbenga, M.D. Ph.D., Department of Internal Medicine and Gynaecology, Reinier de Graaf Hospital, Reinier de Graafweg 5, 2625 AD, Delft, the Netherlands. A.wijbenga@rdgg.nl

45. K. de Boer, M.D. Ph.D., Department of Obstetrics and Gynaecology, Rijnstate Hospital, Wagnerlaan 55, 6815 AD, Arnhem, the Netherlands. kdeboer@rijnstate.nl

46. A. C. Van Bon, M.D. Ph.D., Department of Internal Medicine, Rijnstate Hospital, Wagnerlaan 55, 6815 AD, Arnhem, the Netherlands. acvanbon@rijnstate.nl

47. F.W. van der Made, M.D., Department of Obstetrics and Gynaecology, Franciscus Gasthuis & Vlietland, Kleiweg 500, 3045 PM, Rotterdam, the Netherlands. f.vandermade@sfg.nl

48. S.A. Eskes, M.D. Ph.D., Department of Internal Medicine, Franciscus Gasthuis & Vlietland, Kleiweg 500, 3045 PM, Rotterdam, the Netherlands. s.eskes@franciscus.nl

49. M. Zandstra, M.D., Department of Obstetrics and Gynaecology, Spaarne Gasthuis, Boerhaavelaan 22, 2035 RC, Haarlem, the Netherlands. mzandstra@spaarnegasthuis.nl

50. W.H. van Houtum, M.D. Ph.D., Department of Internal Medicine, Spaarne Gasthuis, Boerhaavelaan 22, 2035 RC, Haarlem, the Netherlands. wvanhoutum@spaarnegasthuis.nl

51. B.A.M. Braams-Lisman, M.D. Ph.D., Department of Obstetrics and Gynaecology , Tergooi, Rijksstraatweg 1, 1261 AN, Blaricum, the Netherlands. Bbraams-lisman@tergooi.nl

52. C.R.G.M. Daemen-Gubbels, M.D., Department of Internal Medicine, Tergooi, Rijksstraatweg 1, 1261 AN, Blaricum, the Netherlands. cdaemen@tergooi.nl

53. M.G.A.J. Wouters, M.D. Ph.D., Department of Obstetrics and Gynaecology, Amsterdam UMC, VU University Medical Center, de Boelelaan 1117, 1081 HV, Amsterdam, the Netherlands. mgaj.wouters@vumc.nl

54. R.G. IJzerman, M.D. Ph.D., Diabetes Center, Department of Internal Medicine, Amsterdam UMC, VU University Medical Center, de Boelelaan 1117, 1081 HB, Amsterdam, the Netherlands. rg.ijzerman@vumc.nl

55. N.A. Mensing van Charante, M.D., Department of Obstetrics and Gynaecology, Dijklander Hospital, Maelsonstraat 3, 1624 NP, Hoorn, the Netherlands. n.a.mensingvancharante@westfriesgasthuis.nl

56. R. Zwertbroek, M.D., Department of Internal Medicine, Dijklander Hospital, Maelsonstraat 3, 1624 NP, Hoorn, the Netherlands. r.zwertbroek@westfriesgasthuis.nl

57. J.E. Bosmans, Ph.D., Department of Health Sciences, Faculty of Science, Vrije Universiteit Amsterdam, Amsterdam Public Health Research Institute, Amsterdam, the Netherlands. De Boelelaan 1081, 1081 BT Amsterdam, the Netherlands. j.e.bosmans@vu.nl

58. I.M. Evers, M.D. Ph.D., Department of Obstetrics and Gynaecology, Meander Medical Center, Maatweg 3, 3813 TZ, Amersfoort, the Netherlands. im.evers@meandermc.nl

59. B.W.J. Mol, M.D. Ph.D., Department of Obstetrics and Gynaecology, Monash University, Monash Medical Centre 246, Clayton Road Clayton, Victoria 3168, Australia. ben.mol@monash.edu

60. H.W. de Valk, M.D. Ph.D., Department of Internal Medicine and Endocrinology, University Medical Center Utrecht, Utrecht University, Lundlaan 6, 3508 AB, Utrecht, the Netherlands. h.w.devalk@umcutrecht.nl

61. F. Groenendaal, M.D. Ph.D., Department of Neonatology, University Medical Center Utrecht, Utrecht University, Lundlaan 6, 3508 AB, Utrecht, the Netherlands. f.groenendaal@umcutrecht.nl

62. C.A. Naaktgeboren, Ph.D., Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Heidelberglaan 100, 3584 CX, Utrecht, the Netherlands. c.naaktgeboren@umcutrecht.nl

63. R.C. Painter, M.D. Ph.D., Department of Obstetrics and Gynaecology, Amsterdam University Medical Centers, University of Amsterdam, Meibergdreef 9, 1105 AZ, Amsterdam, the Netherlands. r.c.painter@amc.uva.nl

64. J.H. DeVries, M.D. Ph.D., Department of Internal Medicine and Endocrinology, Amsterdam University Medical Centers, University of Amsterdam, Meibergdreef 9, 1105 AZ, Amsterdam, the Netherlands. j.h.devries@amc.uva.nl

65. A. Franx, M.D., Ph.D., Department of Obstetrics and Gynaecology, University Medical Center Utrecht, Utrecht University, Lundlaan 6, 3508 AB, Utrecht, the Netherlands. a.franx-2@umcutrecht.nl

66. B.B. van Rijn, M.D. Ph.D., Department of Obstetrics and Gynaecology, University Medical Center Utrecht, Utrecht University, Lundlaan 6, 3508 AB, Utrecht, the Netherlands. Department of Obstetrics and Prenatal Medicine, Erasmus MC University Medical Center Rotterdam, Doctor Molewaterplein 40, 3015 GD, Rotterdam, the Netherlands. b.vanrijn@erasmusmc.nl

Corresponding author
B.B. van Rijn, M.D., Ph.D.
Department of Obstetrics & Prenatal Medicine
Erasmus MC University Medical Center Rotterdam
Doctor Molewaterplein 40
3015 GD, Rotterdam, the Netherlands
b.vanrijn@erasmusmc.nl

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ABSTRACT

Introduction: In women with gestational diabetes mellitus (GDM) requiring pharmacotherapy, insulin was the established first-line treatment. More recently oral glucose lowering drugs (OGLDs) have gained popularity as a patient-friendly, less expensive, and safe alternative. Monotherapy with metformin or glibenclamide (glyburide) is incorporated in several international guidelines. In women who do not reach sufficient glucose control with OGLD monotherapy, usually insulin is added, either with or without continuation of OGLDs. No reliable data from clinical trials, however, is available on the effectiveness of a treatment strategy using all three agents: metformin, glibenclamide, and insulin, in a stepwise approach, compared with insulin-only therapy for improving pregnancy outcomes. In this trial we aim to assess the clinical effectiveness, cost-effectiveness and patient experience of a stepwise combined OGLD treatment protocol, compared to conventional insulin-based therapy for GDM.

Methods: The SUGAR-DIP trial is an open label, multicenter randomized controlled non-inferiority trial. Participants are women with GDM who do not reach target glycemic control with modification of diet, between 16-34 weeks of gestation. Participants will be randomized to either treatment with OGLDs, starting with metformin and supplemented as needed with glibenclamide, or randomized to treatment with insulin. In women who do not reach target glycemic control with combined metformin and glibenclamide, glibenclamide will be substituted with insulin, while continuing metformin. The primary outcome will be the incidence of large-for-gestational-age infants (birth weight >90th percentile). Secondary outcome measures are maternal diabetes-related endpoints, obstetric complications, neonatal complications and cost-effectiveness analysis. Outcomes will be analyzed according to the intention-to-treat principle.

Ethics and dissemination: The study protocol was approved by the Ethics Committee of the Utrecht University Medical Center. Approval by the boards of management for all participating hospitals will be obtained. Trial results will be submitted for publication in peer-reviewed journals.

Trial registration: Netherlands Trial Registry NTR6134 (November 2016).

Keywords: gestational diabetes mellitus, oral glucose lowering drugs, antihyperglycemic agents, antidiabetic medication, metformin, glyburide, glibenclamide, insulin, randomized controlled trial, large-for-gestational-age.

Article summary:

Strengths and limitations of this study

- This is the first open-label randomized controlled trial that directly compares a step-wise treatment protocol using a combination of oral glucose lowering drugs (OGLDs) to insulin as a first-line treatment for GDM not responding to diet
- The randomized multi-center design minimizes the risk of bias and increases generalizability of the results
- Variation in diagnostic thresholds and treatment targets for GDM may need to be addressed to assess the value of this strategy across different populations

INTRODUCTION:

The prevalence of gestational diabetes mellitus (GDM) is rising and currently affects approximately 1-28% of all pregnancies, varying by region and diagnostic criteria used.[1–4] GDM carries significant perinatal risks for pregnancy and childbirth, such as polyhydramnios, small- and large-for-gestational-age infants, macrosomia, stillbirth, shoulder dystocia, obstructed labor, preeclampsia and neonatal hypoglycemia.[5–9] In addition, increasing concern exists about the impact of GDM on offspring development and associated long-term risks for glucose and insulin resistance, obesity and chronic disease in children born to mothers with GDM.[10–12]

The rising number of women diagnosed with GDM is increasingly putting pressure on health care resources. Effective treatment for GDM treatment requires a multidisciplinary approach by midwives, obstetricians, dieticians, endocrinologists, and diabetes nurse specialists. Current treatment of GDM focuses on achieving optimal glycemic control. When blood glucose levels, usually based on self-monitoring, fall outside the target range despite lifestyle- and dietary advice, treatment with antihyperglycemic medication is indicated.[13,14] As pharmacologic treatment subcutaneous insulin injections have traditionally been used as first-choice treatment for GDM and is still advocated in many [15–18], but not all guidelines [19–21]. In recent years, clinical research and experience with oral glucose lowering drugs (OGLDs) has shown promising results as a treatment alternative that may substitute insulin in many women.[22,23]

Metformin and glibenclamide (glyburide) are the OGLDs most studied for diabetes in pregnancy. Both are already widely used in the treatment of GDM, considered to be safe and have been incorporated in several guidelines as treatment options alongside insulin.[19–21,24,25] A 2014 retrospective cohort study from the United States showed that the use of glibenclamide had increased from 7.4% in 2000 to 64.5% in 2011, becoming the most common treatment for GDM requiring pharmacotherapy in 2007.[26] In the United Kingdom, incorporated in the NICE guidelines (National Institute for Health and Care Excellence, UK),

metformin is the first choice treatment, supplemented with insulin if needed.[19] Insulin is offered to women if metformin is contraindicated or unacceptable to the patient, or target glucose values are not met with metformin only. The NICE guidelines state that glibenclamide could be considered an option for women in whom blood glucose targets are not achieved with metformin, but decline insulin therapy, or for those who cannot tolerate metformin. The International Federation of Gynecology and Obstetrics (FIGO) and more recently the Society of Maternal-Fetal Medicine (SMFM) Committee further endorsed OGLDs as a reasonable and safe first-line pharmacologic treatment option in GDM, with metformin being preferred over glibenclamide.[21,25] In contrast, in the Netherlands, insulin has remained the drug of choice in the majority of hospitals.

Two 2017 Cochrane Reviews on 11 and 53 studies (1487, and 7381 women) concluded that due to insufficient high-quality evidence no single agent is superior in the treatment of GDM.[27,28] And although the use of OGLDs is widespread, there is an ongoing discussion on which drug should be first line treatment after lifestyle- and dietary interventions.[24] Both insulin and oral agents have advantages and disadvantages. Insulin is safe and effective, however is considered burdensome by pregnant women, requires intensive glucose monitoring, and is associated with episodes of maternal hypoglycemia.[29] OGLDs are less costly, less burdensome and associated with higher patient satisfaction.[23,30–33] Metformin has the advantage over insulin that hypoglycemic events do not occur, but it is less potent when compared to glibenclamide, can cause gastro-intestinal side-effects and is possibly associated with more spontaneous preterm deliveries.[34] Glibenclamide, similar to insulin, is more potent in its glucose-lowering effect and may cause hypoglycemia in the mother and newborn.[22,35] Other undesirable effects include gastro-intestinal reactions, allergic skin reactions, altered liver enzyme values, visual disturbances and weight gain. And although intrauterine exposure to metformin or glibenclamide is not associated with congenital anomalies, much less is known about direct fetal metabolic effects and long-term effects on mothers and offspring.[36]

With current OGLD monotherapy, consisting of either metformin or glibenclamide, in women who do not reach glycemic control, prompting the need for additional measures, in general OGLDs are replaced by or supplemented with insulin. A combination of oral agents may be an interesting strategy for GDM treatment, however current evidence is insufficient to determine the optimal use of OGLDs. In a recent randomized controlled trial by Nachum *et al.* in 104 women with GDM, powered for glycemic control, combination therapy of metformin and glibenclamide decreased the need for additional insulin from 32% to 11% (p = 0.0002) compared to monotherapy.[37] Metformin as the first-line therapy combined with glibenclamide if needed was associated with the highest treatment success. These data support the need for a well-powered large scale randomized controlled trial to compare a step-wise approach combining metformin and glibenclamide to conventional insulin therapy to study effects on pregnancy outcomes.

In the SUGAR-DIP trial, a multicenter randomized controlled trial, we aim to assess non-inferiority of treatment with metformin, and in case of insufficient glycemic control the addition of glibenclamide, compared to immediate insulin in the treatment of GDM. We expect that a proportion of patients will achieve glycemic control with metformin only. By adding glibenclamide in combined treatment with metformin, we expect to achieve glycemic control as good as by insulin, while maintaining the benefits and ease of a less burdensome treatment with oral medication. We will assess the clinical effectiveness, cost-effectiveness and patient experience of stepwise oral antihyperglycemic medication to treat GDM compared to conventional insulin-based treatment strategy.

METHODS:

Design and setting:

The SUGAR-DIP trial is a multicenter non-inferiority randomized controlled trial (RCT). The study will be open label as oral drugs and insulin cannot be administered individually in a blinded way. The study will be conducted within the setting of the Dutch Consortium for Healthcare

Evaluation and Research in Obstetrics and Gynaecology – NVOG Consortium 2.0,[38] a collaborative network of all major hospitals in the Netherlands and the Dutch Society of Obstetrics and Gynaecology (NVOG) and performed by treatment teams generally consisting of an internist, a gynaecologist and diabetes nurses. The trial was approved by the Medical Research Ethics Committee (MREC) of the UMC Utrecht. Trial reference number: 16-523/M. The trial is registered in the Netherlands Trial Registry on 29 November 2016 under the number NTR6134.[39]

Patient and public involvement:

In the preparation of the trial, the patient organisation Dutch Diabetes Association (Diabetes Vereniging Nederland) was involved. A questionnaire on patient perspectives of women who have (had) GDM was issued by the organization prior to the development of the study protocol. The organization was furthermore involved in reviewing the study protocol and provided valuable input in the development of the information material used in the study. Upon completion of the trial the patient organisation will be involved in dissemination of the study results.

Participants and eligibility criteria:

Women diagnosed with GDM who have not reached target glycemic control with dietary and lifestyle adaptations and thus meet the criteria for additional treatment with antihyperglycemic medication between 16 to 34 weeks of gestation, will be eligible for inclusion. Target glycemic control is defined by the NVOG (Dutch College O&G) diabetes in pregnancy guideline as a fasting glucose concentration $\leq$5.3 mmol/L, 1-hour postprandial $\leq$7.8 mmol/L or 2-hour postprandial $\leq$6.7 mmol/L.[18]

The diagnosis of GDM is made according to Dutch national guidelines, using a 75-gram oral glucose tolerance test.[18] Due to a transition in diagnostic thresholds, both the WHO 1999 (fasting $\geq$7.0 mmol/L or 2-hour postload $\geq$7.8 mmol/L) and WHO 2013 criteria (fasting $\geq$5.1 mmol/L, 1-hour postload $\geq$10.0 or 2-hour postload $\geq$8.5 mmol/L) for venous plasma glucose

values were used to diagnose GDM. The 100-gram OGTT is incorporated in the study protocol, as it is part of the Dutch national guideline, however this test is not commonly used in the Netherlands. Although thresholds for the diagnosis of GDM in the Netherlands and therefore in the trial are divergent to some extent, the target glucose values to define insufficient glycemic control (while on diet) as the additional inclusion criterium for enrolment in the trial apply to all centers. It is thus expected that patients eligible for enrolment form a homogenous group despite differences in screening tools.

Screening in the Netherlands is conducted according to a high risk strategy, and takes place in the second trimester (24-28 weeks) among pregnant women with one or more of the following risk factors: a history of GDM, BMI>30 (kg/m^2), a history of a neonate with a birth weight >95th percentile or >4500 grams, a first degree family member with diabetes, polycystic ovary syndrome, a history of an unexplained intra-uterine death or an ethnicity with higher diabetes risk (e.g. women from South-Asia, Indian descent / Surinamese, Afro-Caribbean, Middle-Eastern, Moroccan or Egyptian ethnicity). In case of a history of GDM in a previous pregnancy an OGTT as early as 16 weeks of gestation is recommended, to be repeated at 24-28 weeks if normal. An OGTT may furthermore be performed in case of suspected fetal macrosomia, polyhydramnios, or symptoms of polydipsia or polyuria, also in women without risk factors.

For the SUGAR-DIP trial we have set the upper limit for inclusion to 34 weeks, in line with previous trials [22,23,40], allowing for at least 4 weeks of exposure to pharmacological treatment. With the timing of the OGTT in current guidelines it is expected that the majority of women will be treated for over 8 weeks. Although in women diagnosed later in pregnancy exposure to treatment may have less of an effect on the primary outcome, treatment may still influence several important secondary outcomes, such as neonatal hypoglycemia.

Additional inclusion criteria for the SUGAR-DIP trial are: (1) maternal age $\geq$18 years (2) singleton pregnancy (3) ability to understand the Dutch or English language and (4) ability to provide written informed consent. Patients who meet any of the following criteria are excluded from the

study: (1) known pre-existing type 1 or type 2 diabetes mellitus (2) severe medical or psychiatric comorbidities (3) significant liver disease or renal insufficiency, or any other known condition with contraindications for the use of either metformin or glibenclamide (4) pregnancy with a fetus affected by major congenital birth defects and/or chromosomal abnormality.

Recruitment and randomisation:

Eligible women will be informed and invited to participate by either their diabetes care or obstetric care provider, i.e. physician, obstetrician, midwife, or diabetes nurse. Following counselling, written informed consent is obtained and participants are individually randomized to either stepwise OGLDs or insulin. Randomization is performed through a central web-based tool (Castor EDC, Ciwit B.V., the Netherlands and Castor Research Inc, USA), using a 1:1 ratio and block randomization with a variable block size of 4 and 6.

Intervention and control:

The stepwise treatment strategy for the intervention (OLGD) and control (insulin) group is displayed in Figure 1.

Oral glucose lowering drugs (OGLDs):

In women allocated to the OGLD strategy, metformin is initiated with a starting dose of 500 mg once daily for 3 days, followed by an increase of 500 mg every 3 days to the final daily dose of 2000 mg divided into 2 doses. In case of serious side effects (e.g. severe nausea, persistent vomiting or diarrhoea), the metformin dose can be lowered to the maximum dose tolerated with acceptable side effects. Participants are advised to take metformin during or shortly after a meal to reduce side effects. In case of insufficient glycemic control with metformin at the maximum (tolerated) dose, glibenclamide will be added at a starting dose of 2.5 mg once daily. Glibenclamide can be increased if glycemic goals are not met with increments of 2.5 mg every week, up to a maximum dose of 15 mg daily. In case of insufficient glycemic control with both metformin and glibenclamide at the maximum doses, glibenclamide will be discontinued and replaced by insulin, while metformin will be continued.

Insulin:

Participants randomized to insulin treatment will receive insulin according to usual practice, i.e. in incremental doses until glycemic targets are met.[41] This includes both short- and long-acting insulin.

Study procedures:

Diabetes care:

In all participants, a specialized diabetes nurse or internal medicine specialist will review glycemic control every 1-2 weeks using the following target values for glucose, as measured by capillary glucose self-testing: fasting $\leq$ 5.3 mmol/L, 1 hour postprandial $\leq$ 7.8 mmol/L and 2 hours postprandial $\leq$ 6.7 mmol/L. If titration of medication requires more frequent feedback, participants will be given the option to contact their diabetes treatment specialist in between scheduled visits. All participants receive the usual instructions regarding hypoglycemic events (glucose <4.0 mmol/L). A participant diary is used to document glucose values and medication use, and is reviewed at every visit. Frequency of self-monitoring will be discussed on an individual basis with the treating diabetes team. Weight is documented at study inclusion and at every subsequent visit. Blood sampling for glycated haemoglobin (HbA1c) is performed at study inclusion, at 30 weeks and at 36 weeks of pregnancy.

Obstetric care:

All participants will receive obstetrical care based on usual practice for gestational diabetes mellitus requiring pharmacological therapy. This includes assessment of fetal biometry at weeks 26-28, 30-32 and 34-36 of pregnancy by measuring fetal abdominal circumference (AC), femur length (FL), head circumference (HC), estimated fetal weight (EFW) (Hadlock or similar) and amniotic fluid volume. The timing of delivery follows local protocol, based on national guidelines.[18] Induction of labour around 38-39 weeks of gestation is generally recommended for women with GDM requiring medication. Both oral antihyperglycemic agents and insulin may

be discontinued on the day of delivery in case of induced labor or as soon as labor is established after spontaneous onset. Monitoring of glucose levels during labor is advised.

Neonatal care:

Neonatal glucose monitoring will be performed serially for up to 12-24 hours after delivery in accordance to local protocol in participating sites. We defined neonatal hypoglycemia as a plasma glucose concentration <2.6 mmol/L and severe neonatal hypoglycemia as <2.0 mmol/L.[42] Time and plasma glucose values are documented as well interventions used to regulate neonatal glucoses. Furthermore, any admission to a neonatal Medium Care or Intensive Care Unit is documented.

Postpartum:

Participants will attend routine obstetric and diabetes care provider appointments around 5-6 weeks postpartum at which time glucose self-monitoring will be carried out to detect persistent postpartum hyperglycemia.

Outcome measures

Primary outcome measure:

The primary outcome is a large-for-gestational-age (LGA) infant. Large-for-gestational-age is defined as a birth weight $\geq 90^{th}$ percentile, using the Dutch Perinatal Registry (PRN) reference charts.[43]

Secondary outcome measures

Secondary outcomes include maternal hypoglycemia (biochemical hypoglycemia <3.9 mmol/L, symptomatic hypoglycemia, severe hypoglycemia prompting the need for help by another person and/or hospital admission for hypoglycemia), elective- and emergency Caesarean section, pregnancy related hypertensive disorders including Pregnancy Induced Hypertension (PIH) and preeclampsia (PE), preterm delivery (delivery <37 weeks of gestation), postpartum neonatal hypoglycemia (moderate: serum glucose <2.6 mmol/L, severe: serum glucose <2.0

mmol/L), neonatal hyperbilirubinemia requiring phototherapy, neonatal Medium Care or Intensive Care admission and a cost-effectiveness analysis. These secondary outcomes were selected based on their clinical relevance and/or observed differences in previous studies comparing OGLDs and insulin.

Furthermore, a number of maternal baseline characteristics, additional obstetric- and neonatal outcomes, diabetes-related endpoints, biomarkers and laboratory examinations will be assessed *(see supplement 1 and 2)*.

Follow-up

Details regarding outcomes, including maternal and neonatal hospital admissions or complications are recorded up to 6 weeks postpartum. Long-term follow-up of mother and child is not part of the initial trial, however participants will be informed about planned long-term follow-up and asked to provide additional personal information and contact details on the patient information and informed consent form at study inclusion.

Patient perspective and treatment satisfaction:

Side effects will be monitored using a custom made form consisting of a short list of the most common side effects and the possibility to self-report any other experienced undesirable effects. The form will also address the actions taken as a response to side effects. Both treatment arms receive the same side effect form. Furthermore, treatment satisfaction is measured around 36 weeks of pregnancy using the Diabetes Treatment Satisfaction Questionnaire (DTSQ), consisting of 8 questions regarding diabetes treatment and patient experience.[44,45] Two additional questions regarding the impact of side effects and discomfort were provided by the copyright holder from a related treatment satisfaction measures for another condition, and added as items 9 and 10 of the DTSQ, to be analysed separately.[46]

Safety and monitoring:

An independent Data and Safety Monitoring Board (DSMB) will be established to safeguard the interests of trial participants, assess the safety and efficacy of the interventions during the trial

period and monitor the overall conduct of the clinical trial. An interim safety review is planned at 300 included participants and will be carried out by an independent statistician.
All serious adverse events (SAE) reported by the subject or observed by the investigator or staff will be recorded. SAE definitions and standards for expedited reporting follow the ICH GCP guidelines on safety reporting.[47] All SAEs will be reported to the accredited ethics committee that approved the protocol, according to the requirements of that committee.

Sample size:

The primary outcome measure, rate of LGA infants, is anticipated to occur in 20% of patients in both study groups, based on a Dutch study cohort.[48] We have set the non-inferiority limit at 8%, which is equivalent to excluding a relative risk in the OGLD treatment compared with conventional insulin-based therapy greater than 1.4. With a one-sided significance level (α) of 0.025 and a power of 0.8, the sample size is calculated at 393 patients in each arm. Accounting for a loss to follow-up of 3%, 810 patients are needed (405 per arm).

Analyses and reporting of results:

Primary and secondary outcomes:

Primary analysis of the RCT results will be according to the intention-to-treat principle. Missing data will be handled according to the complete-case analysis principle, based on the availability of the components needed to determine the primary endpoint. Results will be reported according to CONSORT guidelines, using the extension for non-inferiority trials. In case of substantial cross-over (>5%), a per protocol analysis is used additionally to the intention-to-treat analysis. Cross-over is defined as patients not receiving the treatment allocated by randomization (e.g. participant never started treatment, treatment is no longer necessary for instance due to improved dietary adaptations, side-effects, or stopping treatment shortly after randomization).

For the primary analysis, the non-inferiority of metformin/glibenclamide versus insulin for preventing large-for-gestational-age infants will be established when the upper bounds of the

two-sided 95% confidence interval for the risk ratio is less than 1.4. Large-for-gestational-age will be defined as birth weight >90th percentile.[43] Results for the primary outcome will also be presented as absolute and relative risks (along with 95% confidence intervals (CI)) and numbers needed to treat (if applicable). Analyses will not be adjusted for any observed differences in baseline characteristics between the arms.

The secondary outcome measures will be analysed similar to the primary outcome measure. Categorical secondary outcomes will be assessed by comparing the event rates in the two groups using a chi-square test with a p-value of 0.05 and also by presenting absolute and relative risks. For continuous secondary outcomes, differences between groups will be assessed with the student's t-test if the outcome is normally distributed and with a non-parametric Mann-Whitney U test if skewed. These outcomes will be presented per group as means with standard deviation, geometric means with 95% CI, or as median with interquartile range, depending on distribution.

Subgroup analyses:

Subgroup analyses will be performed for women with and without a history of GDM, a family history of diabetes mellitus (first and/or second degree relative), BMI (normal weight, overweight, obese), according to severity of GDM (fasting and 2 hour OGTT glucose value by various diagnostic criteria and cut-offs), sex (neonate). Additionally, potential causes for treatment failure of metformin alone will also be explored. Within the patients receiving oral agents, the outcome rate will be compared between the patients whose blood glucose could be regulated by metformin alone and those patients who also required glibenclamide and even additional insulin. Patient characteristics between these groups will be compared to identify possible contributing factors to metformin treatment failure.

Economic evaluation:

An economic evaluation will be conducted alongside the randomized controlled trial according to guidelines issued by the National Health Care Institute.[49] The EuroQuol questionnaire (EQ-

5D-5L) for health status measures is used at time of study inclusion, 36 weeks of pregnancy and 4-6 weeks postpartum.[50] Further Health Technology Assessment questionnaires are based on the iMTA PCQ (Productivity Cost Questionnaire) and MCQ (Medical Consumption Questionnaire), issued at 36 weeks of pregnancy and 4-6 weeks postpartum.[51,52] The statistical analysis for the economic evaluation will be done according to the intention-to-treat principle. Missing data will be imputed using multiple imputation. If OGLDs are non-inferior to insulin as hypothesized, a cost minimization analysis will be performed to investigate which intervention is associated with lower costs. If non-inferiority cannot be shown, a cost-effectiveness analysis will be performed. The costs will be analyzed from both a societal (i.e. healthcare costs, patient and family costs, and costs in other sectors) and healthcare perspective (i.e. only healthcare costs). In the cost minimization analysis the differences in costs between OGLDs and insulin will be evaluated using linear multilevel regression models with adjustment for covariates and effect modifiers if necessary. Bootstrapping with stratification for center will be done to estimate 95% confidence intervals around differences in costs. In the cost-effectiveness analysis cost and effect differences will be estimated using seemingly unrelated regression analyses while adjusting for confounders and effect modifiers if necessary. Incremental cost-effectiveness ratios (ICERs) will be calculated by dividing the difference in mean total costs between the treatment groups by the difference in mean effects. Bootstrapping with stratification for center will be used to estimate uncertainty surrounding the ICERs. Uncertainty surrounding the ICERs will be graphically presented on cost-effectiveness planes. Cost-effectiveness acceptability curves showing the probability that the intervention is cost-effective in comparison with usual care for a range of different ceiling ratios will also be estimated.[53] A sensitivity analysis will be performed to investigate the robustness of the results to variation in the most influential cost parameters such as medication and time required for clinical consults.

Data handling:

Baseline data including patient demographics, obstetric and medical history, details regarding the pregnancy, delivery outcomes and diabetes treatment will be recorded using a web-based electronic case record form (eCRF) using Castor EDC. The eCRF is based on a standardized

piloted eCRF that has been used in other multicenter trials within the NVOG Consortium 2.0 network and will be filled in by trained research nurses. The full eCRF is provided as a supplemental file (*Supplement 2*). A study monitor will periodically visit participating centres, assessing quality of data and auditing trial conduct. Patient privacy will be ensured by allocation of unique participant numbers, which will be used on all study documentation. The participant code is only available to the local investigator and research staff.

Ethics and dissemination

This trial has been approved by the Medical Research Ethics Committee (MREC) of the UMC Utrecht. Trial reference number: 16-523/G-M-X. The MREC of the UMC Utrecht is accredited by the Central Committee on Research Involving Human Subjects (CCMO) since November 1999. For all participating hospitals and study sites approval by the boards of management will be obtained. The CCMO has issued a 'No grounds for non-acceptance' for the SUGAR-DIP trial. Research with a medicinal product must undergo an extra, marginal review alongside the review by the reviewing party (MREC). The competent authority (CCMO) checks if there are 'motivated objections' against the study. For this the European adverse reactions database (EudraVigilance) is checked for any previously reported suspected adverse reactions to the medicinal product, which could lead to unacceptable risks to the participating research subject. Furthermore, the CCMO is responsible as the competent authority for entering data into the European EudraCT database. EudraCT number for this trial: 2016-001401-16.

Changes to the study protocol are documented in amendments. Amendments are submitted for approval to the MREC. Major changes will be updated on the trial registration website.[39] The full study protocol, including amendments, is publically available on the study website.[54]

After completion of the trial the principal investigator will report on the results of the main study and submit a manuscript to a peer-reviewed medical journal. Supplementary analyses will be reported separately.

Data availability statement:

The datasets used and/or analyzed during the current study will be made available from the corresponding author on reasonable request.

Author contributions:
Study concept, trial design and study protocol: LW, DNV, JEB, IME, BWM, HWV, FG, CAN, RCP, JHD, AF, BBR
Acquisition of data: LW, DR, BMCA, RMKK, RCP, MRS, MALVD, FA, DHS, MARV, SMIK, MMO, JJZ, MJMD, TEV, PRJG, SG, WV, NH, TKK, RL, RH, AJMH, TB, CAM, AWB, WH, SV, AGVV, RCD, HJJ, MS, EJPK, JOEHL, PWP, IME, MESP, ESA, CBB, BBH, BJP, OWHH, BG, ML, JAW, KB, ACB, FWM, SAE, MZ, WHH, BAMBL, CRGMDG, MGAJW, RGIJ, NAMC, RZ
Analysis and interpretation of data: LW, DR, DNV, JEB, IME, BWM, HWV, FG, CAN, RCP, JHD, AF, BBR
Drafting of the manuscript: LW, DR, CAN, RCP, JHD, AF, BBR
Critical revision of the manuscript for important intellectual content: LW, DR, DNV, JEB, IME, BWM, HWV, FG, CAN, RCP, JHD, AF, BBR, BMCA, RMKK, MRS, MALVD, FA, DHS, MARV, SMIK, MMO, JJZ, MJMD, TEV, PRJG, SG, WV, NH, TKK, RL, RH, AJMH, TB, CAM, AWB, WH, SV, AGVV, RCD, HJJ, MS, EJPK, JOEHL, PWP, MESP, ESA, CBB, BBH, BJP, OWHH, BG, ML, JAW, KB, ACB, FWM, SAE, MZ, WHH, BAMBL, CRGMDG, MGAJW, RGIJ, NAMC, RZ
Study supervision: JHD, AF, BBR

Trial Sponsor:
Institution: University Medical Center Utrecht, Wilhelmina Children's Hospital
Principal investigator: Prof. Dr. A. Franx
Address: Lundlaan 6, 3584 EA, Utrecht, the Netherlands

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Competing interests:
JHD sits on advisory boards for Novo Nordisk A/S
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BWM reports consultancy for ObsEva, Merck KGaA and Guerbet

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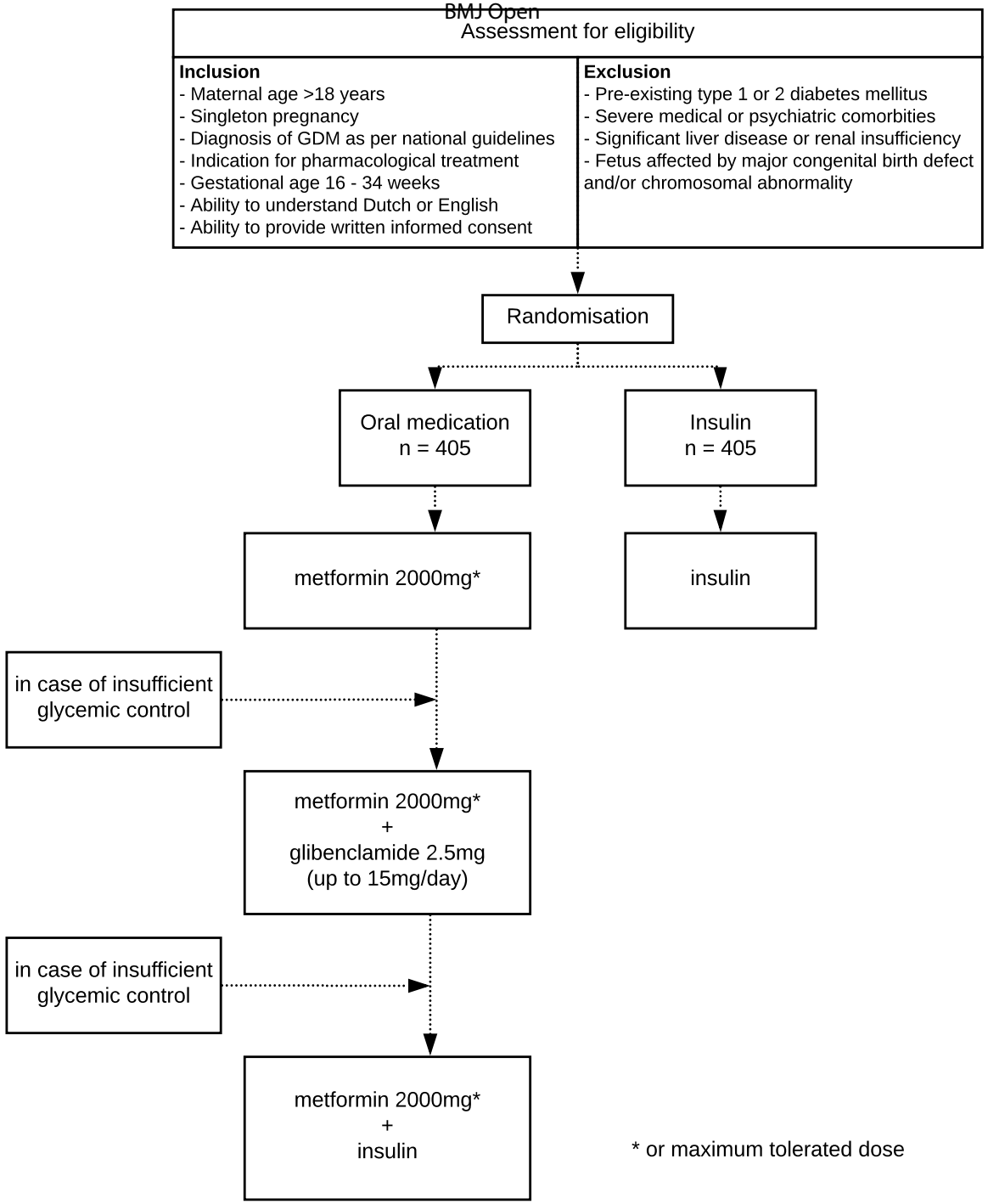
FIGURE HEADINGS:

FIGURE 1:

Figure I: flowchart of comparator (oral glucose lowering drugs) versus control (insulin)



Supplemental file 1: SUGAR-DIP additional study parameters and endpoints

Maternal baseline characteristics

- BMI at study entrance
- Age (y)
- Parity
- Mean arterial blood pressure at study entry (mmHg)
- Intoxications (smoking, alcohol use)
- Ethnicity: Caucasian, Indian/Pakistani/Bangladesi, Afro-Caribbean (Antilles, Surinam-creole), Hindu/Caribbean (Surinam Hindu), African (Sub-Sahara), Middle Eastern/North African (Turkish, Moroccan), Asian, Other
- PCOS; polycystic ovarian syndrome
- Thyroid problems: hypo- or hyperthyroidism
- History of gestational diabetes mellitus
- History of psychological problems
- Family history: diabetes mellitus, gestational diabetes, hypertension, preeclampsia, congenital defects
- Conception: spontaneous, fertility treatment (clomifene citrate, gonadotropins, IVF, ICSI)
- Reason for GDM screening
- Blood glucose measures of OGTT (fasting, post load)
- Gestational age at time of OGTT

Neonatal characteristics

- Gestational age at delivery
- Birth weight (g)
- Weight at discharge (g)
- Sex
- Apgar score 5 – 10 minutes
- Umbilical artery pH levels
- Respiratory support > 24 hours
- Culture proven sepsis
- Neonatal blood glucose levels 1-3-6-12 (24) hours after delivery
- Intravenous glucose therapy
- Convulsions
- Intrauterine fetal death
- Neonatal death
- Congenital defect/anomaly

Obstetric / delivery characteristics

- Ultrasound examinations: fetal biometry (abdominal circumference, femur length, head circumference, estimated fetal weight) amniotic fluid, fetal heart and brain (where available)
- Induction of labour
- Birth injury: shoulder dystocia (a delivery that requires additional obstetric maneuvers following failure of gentle downward traction on the fetal head to effect delivery of the shoulders), clavicle/humerus fracture or Erb's palsy
- Vacuum assisted delivery
- Blood loss (ml)
- Post-partum haemorrhage >1L
- Blood transfusion
- Sphincter rupture

Diabetes related endpoints

- Ketoacidosis
- Fasting and postprandial blood glucose levels (study diary)
- Maternal HbA1c (study inclusion, 30 weeks and 36 weeks of gestation)
- Maternal weight gain >12kg
- Final daily dose of insulin (study diary)
- Final daily dose of metformin/glibenclamide (study diary)
- Time to reach glycemic control (study diary)
- Treatment failure: percentage of patients requiring insulin after metformin and glibenclamide
- Side effects: metformin, glibenclamide, insulin

Biomarkers and laboratory measurements

- Cord-blood: C-peptide, glucose, insulin, triglycerides (where available)
- Cord-blood: metformin / glibenclamide levels (where available)
- Placenta: pathological examination (where available)

Biobanking (where available)

- Maternal serum
- Placental biopsies
- Umbilical cord blood
- Umbilical cord tissue

SUGAR-DIP trial

Oral medication strategy versus insulin for diabetes in pregnancy

Electronic case report form

CRF data entry and randomization:

www.castoredc.com

o Single possible answer
□ Multiple answers possible

General information	
Maternal age at time of randomization	(years)
Estimated date of delivery	(dd-mm-yyyy)
In-exclusion	
Age 18 years or older	o Yes o No
Singleton pregnancy	o Yes o No
Diagnosis if gestational diabetes mellitus as per national guidelines	o Yes o No
Indication for pharmacological treatment of GDM	o Yes o No
Gestational age between 16 and 34 weeks	o Yes o No
Ability to understand Dutch or English	o Yes o No
Known pre-existent type I or II diabetes mellitus	o Yes o No
Severe medical or psychological comorbidity	o Yes o No
Liver disease or kidney failure, or any other condition with contraindications for the use of either metformin or glibenclamide	o Yes o No
Fetus with major congenital birth defect and/or chromosomal abnormality	o Yes o No
Informed consent & Randomization	
Patient has provided written informed consent	o Yes o No
Date of informed consent	(dd-mm-yyyy)
Date of randomization	(dd-mm-yyyy)
Gestational age at time of randomization	….. weeks + ….. days
Medical history	
Ethnicity	o Caucasian/white o Indian/Pakistani/Bangladesi/Hindu o Black/African (Sub-Sahara) o Middle Eastern + North African (Turkey, Morocco, Egypt) o Asian o Other o Unknown
Diagnosis of Polycystic Ovary Syndrome (PCOS)	o Yes o No
Thyroid problems: hypo- or hyperthyroidism	o Hypothyroidism o Hyperthyroidism

	o Thyroid problem, but type is unknown o No o Unknown
History of psychological problems	☐ Depression ☐ Anxiety disorder ☐ Burn-out ☐ Other ☐ None ☐ Unknown
Maternal chronic or pre-existent hypertension	o Yes (requiring medication) o Yes (not requiring medication) o No o Unknown
Maternal medication use (other than folic acid and vitamins) during pregnancy	☐ No ☐ Aspirin (Acetylsalicylic acid) ☐ Levothyroxine / Thyrax ☐ SSRI (including sertraline, (es)citalopram, paroxetine, fluoxetine) ☐ Tricyclic antidepressant (including amitryptiline, nortryptiline) ☐ Other ☐ Unknown
Family history	
Family history of type I / type II diabetes mellitus (1st or 2nd degree)	o Yes o No o Unknown
Family history of gestational diabetes mellitus (1st or 2nd degree)	o Yes o No o Unknown
Family history if hypertension (1st or 2nd degree)	o Yes o No o Unknown
Family history of preeclampsia (1st or 2nd degree)	o Yes o No o Unknown
Family history of congenital defects (1st or 2nd degree)	o Yes o No o Unknown
Obstetric history	
Gravidity	(n)
Parity	(n)
Living children	(n)
Miscarriage – spontaneous abortion	(n)
Abortus provocatus – induced abortion	(n)
Extra-uterine gravidity	(n)
Intra-uterine death > 16 weeks	(n)
Any previous pregnancy with gestational diabetes mellitus?	o No (no GDM in previous pregnancies) o Yes o Unknown

How many pregnancies with gestational diabetes mellitus?	(n)
Any pregnancy with GDM treated with insulin?	o No o Yes o Unknown
Any previous pregnancy with pregnancy induced hypertension (PIH)?	o No (no PIH in previous pregnancies) o Yes o Unknown
Any previous pregnancy with preeclampsia (PE)?	o No (no PE in previous pregnancies) o Yes o Unknown
Any previous pregnancy with Hemolysis Elevated Liver enzymes and Low Platelets syndrome (HELLP)?	o No (no HELLP in previous pregnancies) o Yes o Unknown
Any previous pregnancy with a preterm delivery (< 37 weeks of gestation)	o No (no preterm delivery in previous pregnancies) o Yes o Unknown
A caesarean section (primary or secondary) in the past?	o No (no caesarean section in the past) o Yes o Unknown
Any hemorrhagia postpartum (HPP, blood loss ≥ 1000ml) in the past?	o No (no HPP in the past) o Yes o Unknown
Please complete the following questions for all previous pregnancies > 16 weeks	Parity number: …… Gestational age: ….. weeks + ….. days Gender: male, female, unknown Birth weight (grams): …..
Current pregnancy	
Mode of conception	o Spontaneous o Clomifene ovulation induction o Intra-uterine insemination (IUI) o IVF / ICSI o Egg cell donation o Unknown
Maternal height	(cm)
Maternal weight at start of pregnancy	(kg)
Maternal weight at time of study inclusion	(kg)
Maternal weight at time of delivery / last pre-delivery visit	(kg)
Maternal weight gain (total) >12kg	o Yes o No o Unknown
Maternal blood pressure systolic at first antenatal visit	(mmHg)
Maternal blood pressure diastolic at first antenatal visit	(mmHg)
Smoking during pregnancy	o No

	o Quit in first trimester o Quit later in pregnancy o Yes (still smoking) o Unknown
Alcohol use during pregnancy	o Yes o No o Unknown
Glucose value (random) in first trimester	(mmol/L)
Diagnostic test used to determine gestational diabetes	o Oral glucose tolerance test (75 gram) o Oral glucose tolerance test (100 gram) o Fasting glucose level o Glucose day curve o Other
Date of GDM diagnosis	(dd-mm-yyyy)
Glucose value of 75 gram OGTT fasting (laboratory)	(mmol/L)
Glucose value of 75 gram OGTT 2 hours (laboratory)	(mmol/L)
Glucose value of 100 gram OGTT fasting (laboratory)	(mmol/L)
Glucose value of 100 gram OGTT 2 hours (laboratory)	(mmol/L)
Glucose value of 100 gram OGTT 3 hours (laboratory)	(mmol/L)
Glucose value fasting (laboratory)	(mmol/L)
Highest glucose value of glucose day curve	(mmol/L)
Main reason to perform OGTT	o Suspected macrosomia/estimated fetal weight >p90 (current pregnancy) o Family history with diabetes o Obesity o Prior pregnancy with GDM o Ethnicity o Other o Unknown
Pregnancy complications	
Pregnancy induced hypertension (systolic BP > 140mmHg or diastolic BP > 90mmHg)	o Yes o No o Unknown
Pregnancy induced hypertension	o Without medication o With medication (for instance labetolol or methyldopa) o Unknown whether medication was used o Other
Preeclampsia (hypertension with albuminuria)	o Yes o No o Unknown
HELLP	o Yes o No

	o Unknown
Trombo-embolic complications (deep venous thrombosis or lung-embolus)	o Yes o No o Unknown
Hospital admission because of severe glycemic dysregulation	o Yes o No o Unknown
Fetal structural defects (ultrasound)	o Yes o No o Unknown
Fetal structural defects (ultrasound)	☐ Central nervous system, including spina bifida and anencephaly ☐ Skeletal system, including caudal regression syndrome, limb defects and sacral agenesis ☐ Cardiovascular, including transposition of the great vessels, septal defects, single umbilical artery (SUA), coarctation of the aorta ☐ Gastrointestinal, including duodenal atresia ☐ Unknown which system ☐ Other
Macrosomia (EFW >p90 or FAC >p90 or mentioned in conclusion)	o Yes o No o Unknown
Intra-uterine growth restriction (IUGR) (EFW <p10 or FAC <p10 or mentioned in conclusion)	o Yes o No o Unknown
Polyhydramnios (ultrasound)	o Yes o No o Unknown
Oligohydramnios (ultrasound)	o Yes o No o Unknown
Corticosteroid used? (for instance because of imminent premature birth)	o Yes o No o Unknown
Intra-uterine death	o Yes o No
Date of intra-uterine death	(dd-mm-yyyy)
Delivery	
Date of last dose of antidiabetic medication	(dd-mm-yyyy)
Time of last dose of antidiabetic medication	(hh-mm)
Onset of labour	o Spontaneously o Primary caesarean section o Induction
Was induction planned for a different reason than gestational diabetes mellitus?	o Yes o No

	o Unknown
Reason for induction	☐ Elective ☐ Ruptured membranes ☐ Hypertension ☐ Preeclampsia ☐ HELLP syndrome ☐ Maternal: blood glucose dysregulation ☐ Maternal: other → specify ☐ Fetal: suspected macrosomia ☐ Fetal: suspected intra-uterine growth restriction ☐ Fetal: no movements ☐ Fetal: heart rate anomaly ☐ Fetal: oligohydramnios ☐ Fetal: meconium ☐ Fetal: other → specify ☐ Other → specify
Method of induction	☐ Foley catheter / mechanical ☐ Prostaglandins ☐ Amniotomy ☐ Oxytocin ☐ Other ☐ Unknown
Indication for primary caesarean section	☐ Elective: breech ☐ Elective: obstetric history (previous caesarean section) ☐ Elective: obstetric history (total sphincter rupture) ☐ Elective: obstetric history (other) ☐ Fetal distress ☐ Fetal: intra-uterine growth restriction ☐ Fetal: other ☐ Maternal: hypertension ☐ Maternal: preeclampsia ☐ Maternal: HELLP syndrome ☐ Maternal: other ☐ Unknown
Pain relief during delivery	☐ None ☐ Opioid subcutaneous (pethidine) ☐ Opioid intravenous (remifentanil) ☐ Nitrous oxide ☐ Epidural ☐ Other ☐ Unknown
Medication during labour	☐ Oxytocin ☐ Antibiotics ☐ Tocolytics ☐ Glucose/insulin intravenous ☐ Antihypertensive agents intravenous ☐ Other → specify

	☐ None ☐ Unknown
Fever during delivery	o No o Yes (>38°C <38.5°C) o Yes (≥38.5°C) o Unknown
Fetal presentation	o Cephalic o Breech o Other
Route of delivery	o Vaginal, spontaneously o Instrumental (vacuum extraction) o Instrumental (forcipal extraction) o Secondary caesarean section
Indication for vacuum / forcipal extraction	o Fetal distress o Failure to progress o Maternal indication o Other fetal indication o Unknown
Indication for secondary caesarean section	o Fetal distress o Failure to progress o Failed induction o Maternal indication o Failed vacuum / forcipal extraction o Other fetal indication o Unknown
Were maneuvers used because of shoulder dystocia?	☐ No (no shoulder dystocia) ☐ Traction to the fetal head ☐ McRoberts ☐ Rubin ☐ All-fours ☐ Manual delivery of posterior arm ☐ Intentional breaking of clavicle ☐ Shoulder dystocia but unknown which maneuvers were used ☐ Other
Amniotic fluid	o Clear o Meconium stained o Unknown
Delivery of the placenta	o Spontaneously / controlled cord traction o Manual removal in operating room o Removed during caesarean section o Unknown
Total blood loss	(ml)
Blood transfusion	o Yes o No o Unknown
Perineum	☐ No laceration(s) ☐ First / second degree laceration(s)

	☐ Third degree laceration(s) ☐ Episiotomy ☐ Unknown
Neonatal data	
Date of birth	(dd-mm-yyyy)
Gestational age at birth	….. weeks + ….. days
Live birth	o Yes o No
Neonatal death	o No o Yes (intra-uterine death) o Yes, <24 hours postpartum o Yes, >24 hours postpartum
Gender	o Female o Male o Unknown
Apgar score 1 minute postpartum	
Apgar score 5 minutes postpartum	
Apgar score 10 minutes postpartum	
Umbilical cord blood pH (arterial)	
Umbilical cord blood base excess (arterial)	
Umbilical cord blood pH (venous)	
Umbilical cord blood base excess (venous)	
Birth weight	(grams)
Fracture	☐ None ☐ Humerus ☐ Clavicle ☐ Other ☐ Unknown
Erbs palsy	o No o Yes o Unknown
Preterm birth (<37 weeks of gestation)	o No o Yes (iatrogenic) o Yes (spontaneous)
Neonatal congenital malformation: heart	o No o Yes o Unknown
Neonatal congenital malformation: neural tube	o No o Yes o Unknown
Neonatal congenital malformation: urogenital	o No o Yes o Unknown
Neonatal congenital malformation: other	o No o Yes o Unknown
First neonatal glucose postpartum	(mmol/L)
Date of first neonatal glucose testing postpartum	(dd-mm-yyyy)
Time of first neonatal glucose testing postpartum	(hh:mm)

Second neonatal glucose value postpartum	(mmol/L)
Date of second neonatal glucose testing postpartum	(dd-mm-yyyy)
Time of second neonatal glucose testing postpartum	(hh:mm)
Third neonatal glucose value postpartum	(mmol/L)
Date of third neonatal glucose testing postpartum	(dd-mm-yyyy)
Time of third neonatal glucose testing postpartum	(hh:mm)
Fourth neonatal glucose value postpartum	(mmol/L)
Date of fourth neonatal glucose testing postpartum	(dd-mm-yyyy)
Time of fourth neonatal glucose testing postpartum	(hh:mm)
Fifth neonatal glucose value postpartum	(mmol/L)
Date of fifth neonatal glucose testing postpartum	(dd-mm-yyyy)
Time of fifth neonatal glucose testing postpartum	(hh:mm)
Sixth neonatal glucose value postpartum	(mmol/L)
Date of sixth neonatal glucose testing postpartum	(dd-mm-yyyy)
Time of sixth neonatal glucose testing postpartum	(hh:mm)
Any neonatal glucose value between 2.0-2.6mmol/L (≥2.0 <2.7) during in hospital admission?	o No o Yes, one value between 2.0 and 2.6 o Yes, more than one value between 2.0 and 2.6 o Unknown
Any neonatal glucose value <2.0mmol/L during hospital admission?	o No o Yes, one value <2.0 o Yes, more than one value <2.0 o Unknown
Postpartum	
Were mother or child admitted directly postpartum? (including postpartum observation of mother/child)	o No (mother and child went home directly after delivery o Yes, maternal admission only o Yes, maternal and neonatal admission o Yes, neonatal admission only
Maternal: what was the reason for admission?	☐ Maternal observation/routine stay (for instance because of more blood loss than usual or post-caesarean) ☐ Neonatal observation (for instance because of blood glucose evaluation) ☐ Fluxus (HPP) ☐ Pregnancy induced hypertension ☐ Preeclampsia ☐ HELLP syndrome ☐ Glycemic dysregulation ☐ Thrombo-embolic event

	☐ Hemodynamically unstable (Intensive Care) ☐ Infection ☐ Other
Maternal: type of admission	o Ward o Medium Care o Intensive Care
Maternal: discharge to	o Home o Other ward o Medium Care o Intensive Care o Other hospital
Maternal: date of transfer	(dd-mm-yyyy)
Maternal: type of admission after transfer	o Ward o Medium Care o Intensive Care
Maternal: date of final discharge to home	(dd-mm-yyyy)
Neonatal: what was the reason for admission?	☐ Routine observation for blood glucoses ☐ Routine observation for meconium ☐ Routine observation for suspected infection ☐ Hypoglycemia without i.v. glucose ☐ Hypoglycemia with iv glucose ☐ Hyperbilirubinemia with phototherapy ☐ Hyperbilirubinemia without phototherapy ☐ Respiratory distress syndrome (RDS) / respiratory support or oxygen >24 hours ☐ Broncho pulmonal dysplasia (BPD) ☐ Intraventricular haemorrhage ☐ Sepsis ☐ Necrotizing enterocolitis ☐ Convulsions ☐ Partial exchange transfusion ☐ Trombocyte transfusion ☐ Prematurity ☐ Asphyxia ☐ Other
Neonatal: type of admission	o Ward o Medium Care o Intensive Care
Neonatal: discharge to	o Home o Ward o Medium Care o Intensive Care
Neonatal: date of transfer	(dd-mm-yyyy)
Neonatal: type of admission after transfer	o Ward o Medium Care

	o Intensive Care
Neonatal: date of final discharge to home	(dd-mm-yyyy)
Neonatal weight at time of discharge	(grams)
Did the neonate receive iv glucose infusion postpartum?	o Yes o No o Unknown
How many days of iv glucose infusion?	(days)
Diabetes treatment	
What treatment was the participant randomized to?	o Insulin o Oral hypoglycemic agents
Did the participant ever use: metformin	o Yes o No o Unknown
On which date did the participant start with metformin?	(dd-mm-yyyy)
On which date did the participant stop with metformin?	(dd-mm-yyyy)
Did the participant ever use: glibenclamide	o Yes o No o Unknown
On which date did the participant start with glibenclamide?	(dd-mm-yyyy)
On which date did the participant stop with glibenclamide?	(dd-mm-yyyy)
Did the participant ever use: insulin?	o Yes o No o Unknown
On which date did the participant start with insulin? (If multiple types of insulin were used, use the start date of the first type of insulin)	(dd-mm-yyyy)
On which date did the participant stop with insulin? (If multiple types of insulin were used, use the start date of the first type of insulin)	(dd-mm-yyyy)
Glucose profile most recent before or at randomization: fasting value	(mmol/L)
Glucose profile most recent before or at randomization: after breakfast value	(mmol/L)
Glucose profile most recent before or at randomization: after lunch value	(mmol/L)
Glucose profile most recent before or at randomization: after dinner value	(mmol/L)
Most recent HbA1c value before or at randomization	(mmol/mol)
Date of most recent HbA1c value before or at randomization	(dd-mm-yyyy)
HbA1c value at 30-31 weeks of gestation	(mmol/mol)
Date of HbA1c value at 30-31 weeks of gestation	(dd-mm-yyyy)

HbA1c value at 35-36 weeks of gestation	(mmol/mol)
Date of HbA1c value at 35-36 weeks of gestation	(dd-mm-yyyy)
Additional tests	
Umbilical cord blood C-peptide value	(pmol/L)
Umbilical cord blood glucose value	(mmol/L)
Umbilical cord blood insulin value	(mIU/L)
Umbilical cord blood fructosamine value	(µmol/L)
Umbilical cord blood triglycerides	(mmol/L)
End of study	
Was there a protocol violation?	o No o Yes o Unknown
Did a Serious Adverse Event (SAE) occur during the study until 6 weeks postpartum? (If yes, please report the SAE to the sponsor)	o No o Yes o Unknown
Did a Suspected Unexpected Serious Adverse Reaction (SUSAR) occur during the study until 6 weeks postpartum? (If yes, please report the SUSAR to the sponsor)	o No o Yes o Unknown
Please specify if the subject completed the entire course of the study as specified in the study protocol or discontinued the study:	o Completed o Discontinued
If discontinued, please specify the most appropriate reason for early termination	o Subject violates one or more of the inclusion/exclusion criteria o Adverse event o Participant deceased o Participant lost to follow up o Participant withdrew consent to use personal data o Investigator's and/or physician's decision o Total study is early terminated o Other reason
Has the participant signed informed consent for follow-up?	o Yes o No
Has the participant provided contact information to allow follow-up?	o Yes o No

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Page numbers displayed at each item concern the pages in the protocol manuscript

For applicable items which are not incorporated in the protocol manuscript, we reference to the publically available study protocol document.

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	7 + 13
	2b	All items from the World Health Organization Trial Registration Data Set	Included in registry
Protocol version	3	Date and version identifier	Trial website
Funding	4	Sources and types of financial, material, and other support	22
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1-6 and 21-22
	5b	Name and contact information for the trial sponsor	22
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	NA, investigator initiated

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Publically available study protocol
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	10-12
	6b	Explanation for choice of comparators	10-12
Objectives	7	Specific objectives or hypotheses	12
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	12
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	12
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	13-14
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	14-15
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	14-15
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	15
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	15-16

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	16-17
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	15-17
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	18
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	14

Methods: Assignment of interventions (for controlled trials)

Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	14
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	NA
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	14
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	11
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	29-41
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Publically available study protocol
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Publically available study protocol
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	18-19
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	19
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	18
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Publically available study protocol
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	17
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	17
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	20
Ethics and dissemination			

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	20
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	20
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	13
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Publically available study protocol
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	19-20
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	21
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Publically available study protocol
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Publically available study protocol
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	20
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	20
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	20, study website

Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA_____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.