



Opinion paper

Investigating the role of early low-dose aspirin in diabetes: A phase III multicentre double-blinded placebo-controlled randomised trial of aspirin therapy initiated in the first trimester of diabetes pregnancy

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ABSTRACT

Background: Preeclampsia, preterm birth and low birth weight represent key contributing factors to perinatal morbidity and mortality. Pregnancies complicated by type 1 and type 2 diabetes are at increased risk of these complications, which are purported to be largely attributed to placental dysfunction. Studies investigating a potential role for aspirin therapy in optimizing perinatal outcome have consistently failed to demonstrate a benefit among women with pre-existing diabetes, and yet widespread aspirin administration has become common practice in many centres. This study seeks to examine the effect of aspirin therapy, administered from the first trimester until 36 weeks gestation, on perinatal outcome in women with established pre-pregnancy diabetes. Our hypothesis is that aspirin therapy will reduce complications mediated by placental dysfunction, and improve perinatal outcomes.

Methods: This phase III double-blinded, placebo-controlled randomized clinical trial will be conducted in seven tertiary-level perinatology centres in Ireland. Consenting participants who meet all eligibility criteria will be allocated randomly to either aspirin 150 mg once daily or matching placebo, commenced between 11 + 0 and 13 + 6 weeks. Allocation will take place electronically using software by Clininfo with randomization tables provided by the trial biostatistician. The primary outcome will be a composite clinical measure of placental dysfunction (preeclampsia, preterm birth before 34 weeks, birthweight below the 10th centile or perinatal mortality). This trial has been set up such that it is parallel in design and is a superiority study. No participants have been recruited yet. The trial has been registered with Eudra Clinical Trials - EudraCT Number 2018-000770-29. Funding for this trial was granted by the Health research Board (HRB) 1/9/2017(DIFA-2017-026).

Discussion: Aspirin therapy has been investigated for the prevention of preeclampsia owing to its reduction on thromboxane production. Previous studies have failed to demonstrate a beneficial effect of aspirin on perinatal outcome amongst women with type I or type II diabetes. It is plausible that the failure to observe benefit to date, among the limited aspirin studies that have included participants with diabetes, may be a consequence of aspirin initiation too late in pregnancy to exert any effect on placentation. We believe that if aspirin is to be used for the prevention of placental dysfunction, it must be initiated before the second active phase of trophoblast invasion,

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which takes place from 14 weeks' gestation onwards. No randomized trials investigating the role of aspirin in prevention of preeclampsia in pregnancies complicated by diabetes have previously initiated treatment in the first trimester, the gestational period at which it is most likely to exert an effect on placentation.

1. Background

Pregnant women with pre-existing diabetes are at high-risk for evolution of placenta-mediated complications. Rates of preeclampsia within this group are approximately 20% [1,2]. The National Institute for Health and Care Excellence (NICE) has issued guidance on the prevention of hypertension in pregnancy that includes a recommendation that women deemed to be at high risk for hypertension in pregnancy, such as pregnant women with pre-existing diabetes, be considered for aspirin therapy after 12 weeks gestation. However international guidance is at odds with this such that the Royal College of Obstetricians and Gynaecologists (RCOG), American College of Obstetricians and Gynecologists (ACOG) and Health Service Executive (HSE) do not recommend it.

Pre-existing nephropathy places a woman at particularly high risk for superimposed preeclampsia and for fetal growth restriction. Whether sub-threshold degrees of microvascular disease, as evidenced by microalbuminuria in early gestation, may confer a heightened risk of preeclampsia, is unclear. However whether aspirin therapy may benefit this subgroup with microalbuminuria has not been studied previously.

The combination of diabetes and preeclampsia places the pregnancy at heightened risk for hypoxia and stillbirth. Placental dysfunction, due to disordered early placental development, is central to the disease process [1]. Widespread endothelial dysfunction is the hallmark of preeclampsia, and results in vasoconstriction, ischaemia and increased vascular permeability [2]. While not all adverse perinatal outcomes in diabetes are attributed to placental dysfunction, any therapy that offers the potential to optimise placentation in this group deserves close attention.

Aspirin has been investigated for the prevention of preeclampsia owing to its reduction on thromboxane production. An imbalance between prostacyclin and thromboxane plays a key role in the development of PET and is believed to result from shallow placental invasion and ischaemia that occur shortly after implantation, very early in the first trimester of pregnancy [3].

Studies on the role of aspirin in preventing preeclampsia have produced conflicting results. Initially studies showed a reduced risk [4–6], but larger studies failed to show any benefit [7–9]. A metaanalysis based on 27 trials found aspirin reduced the incidence by 10% [10], but it's authors felt this was too modest to warrant implementation. Of note, among the participants included that had diabetes pre-pregnancy, none were recruited before 16 weeks, so may not have shown the benefit of aspirin.

A large multicentre Maternal-Fetal Medicine Units (MFMU) network study investigated the role of aspirin in preventing preeclampsia and included a subgroup of pregnant women with pre-existing diabetes [2], however they were all recruited in the second trimester. If aspirin is to be used for the prevention of placental dysfunction, theoretically it must be initiated before the second active phase of trophoblast invasion, which takes place from 14 weeks' gestation onwards.

The dose of aspirin used in different trials has varied from 50 to 150 mg. For some women, particularly those with obesity as well as type 2 diabetes, the commonly used 60 mg dose may be too low to produce an adequate response as evidenced by recent work done which indicated 20% of participants in Ireland have an inadequate response to aspirin, as evidenced by thromboxane levels. Their analyses suggested that age, hypertension and weight were the main risk factors to being a non-responder [11].

2. Methods

The aim of this study is to answer the clinical question of whether low-dose antiplatelet therapy (150 mg aspirin) in pregnancy may carry the potential to optimise pregnancy outcome in pregnant women with pre-existing diabetes. Our hypothesis is that aspirin therapy will reduce complications mediated by placental dysfunction, and improve perinatal outcomes.

This is a phase III prospective randomized double-blinded placebo-controlled trial of daily low-dose aspirin 150 mg initiated between 11 and 13 + 6 weeks and continued until 36 weeks of gestation. The trial will be multicentre in seven maternity units in Ireland. This is a parallel study with an allocation ratio 1:1.

This trial was designed according to Consolidated Standards of Reporting Trials (CONSORT) guidelines.

Potential participants are pregnant women that have been diagnosed with diabetes at least 6 months prior to pregnancy. Potential participants will be identified at antenatal clinics and, if they provide informed consent, will be invited to take part in the trial if they meet all inclusion criteria and none of the exclusion criteria.

2.1. Inclusion criteria

- Ability to comprehend the Participant Information Leaflet and to provide signed and dated evidence of informed consent.
- Willing to comply with all study procedures and be available for the duration of the study
- Female, age >18 years
- Singleton pregnancy, ongoing at 11–13 + 6 weeks' gestation
- Diagnosed with diabetes at least 6 months prior to pregnancy
- Fulfillment of each criterion must be clearly evidenced (in lab reports or correspondence) and/or documented in the medical records.

2.2. Exclusion criteria

- Aspirin hypersensitivity (prior bronchospasm/urticarial/angioedema with aspirin)
- Active or recurrent peptic ulceration (2 or more distinct episodes of proven ulceration or bleeding)
- Known bleeding diathesis (hypothrombinaemia, haemophilia, von Willebrands' disease)
- Multifetal gestation
- Breastfeeding
- Severe early-onset preeclampsia in a previous pregnancy
- Participant already on aspirin at the time of screening
- Established chronic kidney disease (progressive loss of renal function of at least 3 months' duration)
- Proteinuria (24-h urinary protein 300g or greater (or spot urinary protein/creatinine ratio >0.3) in the first trimester)
- Chronic hypertension (antihypertensive therapy in first trimester)
- Inability to speak or read English
- SSRI use (current or within last 7 days)
- Inflammatory bowel disease (Crohn's disease or Ulcerative colitis)
- Use of any other investigational medicinal product within the previous 30 days
- The presence of any illness or condition that might interfere with the participant's ability to comply with the study procedures
- Hyperemesis

Following the above, women will be asked to consent in antenatal

clinic by the chief investigator, then enrolled and allocated randomly using the software package Clininfo by either the chief investigator or sub-investigator. No personal information will be collected, participants will be allocated a study number and anonymous otherwise. All data collected will be entered into the eCRF.

Women will be allocated randomly to one of two study groups: low-dose aspirin (150 mg) or placebo once daily from the first trimester (initiated between 11 + 0 weeks and 13 + 6 weeks of gestation) until 36 weeks or sooner if early delivery is planned. The schedule of assessments is as follows: [Table 1](#).

2.2.1. Randomization

Randomization of each study participant will utilize random block sizes (2, 4 and 6) with equal allocation to the study treatment arms (1:1 ratio) within each participating centre. Consequently, the final overall randomized population may not be precisely 1:1. The randomization seed will be stored in the trial master file for the potential situation where the randomization list is required to be re-generated or expanded.

2.2.2. Unblinding

The study code should only be broken for valid medical or safety reasons e.g. in the case of a severe adverse event where it is necessary for the Investigator or treating health care professional to know which treatment the participant is receiving before the participant can be treated. Subject always to clinical need, where possible, members of the research team should remain blinded.

2.2.3. IMP and placebo

The IMP to be used in this trial: Tromalyt® 150 mg prolong release capsule for oral ingestion. The capsule contains 150 mg of anti-platelet agent acetylsalicylic acid, maize starch and Sucrose 20:80. The capsule also contains Copovidone (Kollidon VA-64), Eudragit L, Ethylcellulose and Triacetin. The capsule is made with gelatine, erythrosine, quinoline yellow, titanium dioxide. Tromalyt® is trademark of Meda Pharma SL (Reg 59.210).

Placebos to be used are hard gelatine capsules (Sanitatis®) for participants randomized to the placebo arm. These capsules are externally identical to Tromalyt capsule. The capsules contain 198 mg microcrystalline cellulose and 2 mg of magnesium stearate (Sanitatis®).

Following enrolment participants will be randomly allocated to either aspirin or placebo and baseline investigations will be performed. 4-Weekly study visits will be scheduled until 32 weeks gestation, a 34 and 36 week visit, and then weekly reviews until delivery.

Participants will be instructed to take the Investigational Medicinal Product (IMP) once daily at the same time with water. Participants will be provided with a diary card and instructed to complete the diary each day following administration of medication. Both the diary and the returned IMP will be checked by the Chief Investigator/Principal Investigator (CI/PI) or designee. Any discrepancies which suggest non-compliance will be discussed with the participant during the visit. Ongoing non-compliance may result in the participant being withdrawn from the trial.

2.2.4. Data collection

Data will contemporaneously be collected and inputted to an electronic case report form (CRF) and collected in a central database.

The primary outcome is to investigate the effect of aspirin therapy initiated in the first trimester of pregnancy in women with pre-existing I type I or type II diabetes on a composite clinical outcome of placental dysfunction (preeclampsia, preterm birth less than 34 weeks, birth weight below the 10th centile or perinatal mortality).

Secondary outcomes include will be observational studies and include:

Differences between the intervention and control groups will be measured for the following parameters of neonatal morbidity:

- Gestational age at delivery
- Birth weight
- Neonatal Intensive Care Unit (NICU) admission
- Respiratory morbidity
- Apgar score <7 at 5 min
- Umbilical artery acidosis at birth (cord pH < 7.2)
- Interventricular haemorrhage
- Culture-proven sepsis
- Necrotising enterocolitis
- Hypoxic ischaemic encephalopathy

Differences between the aspirin and control groups will be measured for maternal outcomes not directly related to primary outcome, including:

- Mode of delivery
- Haemorrhage
- Sepsis

The effect of 150 mg aspirin initiated in the first trimester of diabetes pregnancy on microalbuminuria will be evaluated.

Platelet function testing:

Platelet function testing will be performed on study participants at the Rotunda hospital only at 5 time points (pre-treatment, 20, 28 and 34 weeks' gestation and 3–5 days postpartum).

Dynamic platelet function testing will allow the following aspects of antiplatelet therapy in pregnancy to be studied:

2.3. Assessment of participant compliance with the study medication in this subgroup

Evaluation of dynamic changes that may be observed in platelet aggregation with respect to participant-specific variables that may affect platelet biology, such as body mass index (BMI), age, concurrent illness or concomitant medication.

Power analysis is based upon the assumptions that pre-eclampsia has an incidence of approximately 20% in the study population, and that the incidence of preterm delivery before 34 weeks is 4%, birth weight below the 10th centile is 9% and perinatal mortality 3%. Given that outcomes may overlap or co-occur, we assume the baseline rate for the composite outcome of placental dysfunction to be 30%, preeclampsia incidence plus approximately 50% of the remaining outcome rates. A sample size of 283 participants in each arm of the study would be required to demonstrate a 35% reduction in the composite clinical measure of placental dysfunction with 80% power (two-sided type I error 0.05).

We expect to enrol 600 participants in total to allow for drop out and loss to follow-up. Recruitment is expected to take 24 months with each participant enrolled for 36 weeks (30 weeks on the trial medication and 6 weeks postnatal follow up).

Randomization, data management, data quality checks and statistical analysis will be performed by the trial biostatistician, Patrick Dicker (Biostatistician, Royal College of Surgeons in Ireland (RCSI)). The database will be anonymized, encrypted and stored in accordance with data protection law.

All demographics and pregnancy characteristics will be presented according to randomized treatment without formal statistical comparisons. Continuous data will be presented using means, standard deviations, minima, maxima, medians and/or inter-quartile ranges, as appropriate. Frequency tabulations for categorical (nominal and ordinal) data will be presented. Patient disposition will be tabulated and presented as a consort flow diagram.

2.3.1. Primary outcome analysis

Randomization, data management, data quality checks and statistical analysis will be performed by the trial biostatistician, Patrick Dicker (Biostatistician, RCSI). The database will be anonymized, encrypted and

Table 1
Schedule of assessments.

Visit #	Recruitment		Follow Up								
	1	2	3	4	5	6	7	8	9–14	Delivery	Follow-up
Visit Type	Screening period	Baseline	Monthly visit	Monthly visit	Monthly visit	Monthly visits	Monthly visits	2-weekly	Weekly visit	End of study visit	Follow-up visit
Visit schedule	Day –28 to 0	Day 0	Gestation 16weeks ± 7 days	Gestation 20 weeks ± 7 days	Gestation 24 weeks ± 7 days	Gestation 28 weeks ± 7 days	Gestation 32 weeks ± 7 days	Gestation 34 weeks ± 7 days	Gestation 36–40 weeks ± 4 days	² Delivery + max 5 days	³ 6 weeks postpartum ± 2 weeks
Informed Consent	X										
Eligibility determination: medical & obstetric history review/medication review/pregnancy viability (ultrasound), urinary PCR/24-h quantitation/English proficiency	X	¹ X									
Physical exam: weight; otherwise symptom driven	X		X	X	X	X	X	X	X	X	X
FBC, liver profile, serum urea and creatinine	X										
Vital Signs: BP/MAP	X	X	X	X	X	X	X	X	X	X	X
Dipstick urinalysis for proteinuria	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication review	X	X	X	X	X	X	X	X	X	X	X
Urinary PCR/24-h quantitation [4]	X		X		X		X		X	X	X
Platelet function assay (sub-study) [5]		X		X		X		X		X	
Fetal ultrasound: growth, UAD, AFI				X		X			X (36or37)		
Randomization		X									
IMP dispensing (36 tabs)*		X	X	X	X	X	X				
Medication compliance review (pill count)*			X	X	X	X	X	X			
Adverse Events review			X	X	X	X	X	X	X	X	X
Neonatal outcome review (birthweight, NICU admission, respiratory morbidity: need for O2 support, congenital anomaly, and adverse neonatal outcome)										X	X

stored in accordance with data protection law.

Four populations will be described and utilized in the statistical analyses:

- a. All Randomized
- b. Intention-to-treat (ITT): All randomized having a composite outcome measure
- c. Safety Population: All randomized who received at least one dose of study medication
- d. Per-protocol (PP): ITT population excluding major protocol violations and non-compliance with study treatment

Prior to last-patient last-visit an expanded Statistical Analysis Plan will be approved by the Trial Steering Committee.

As per the baseline data, all data collected post-randomization will be summarized using descriptive statistics. Major protocol violations will be listed individually. Safety data (adverse events) will be described in the safety population. Clinical outcomes (primary and secondary) will be described in the ITT and PP populations.

The primary study outcome variable of placental dysfunction will be analyzed using logistic regression with randomized treatment group as a factor (ITT analysis).

The 5% level of significance and 95% Confidence Interval will be used to determine the statistical significance of risk (odds-ratio).

The software SAS version 9.4 will be used for data screening, query resolution and statistical analysis.

Secondary outcome analysis:

Formal secondary outcome analysis (hypothesis tests) will not be performed.

No interim analyses will occur. Recommendations for premature termination of the trial will be described under the terms of the Data Safety and Monitoring Board (DSMB).

After the last-participant-last-visit and resolution of data queries (database-lock), the code break of the randomization will be performed.

Adverse events (AEs):

All AEs occurring during the study observed by the investigator or reported by the subject, whether or not attributed to the study medication, will be recorded on the CRF.

The following information will be recorded: description, date of onset and end date, severity, assessment of relatedness to the study medication, other suspect medication or device and action taken and outcome. Follow-up information should be provided as necessary.

All AEs will be recorded in the medical records and CRF following consent. Clinically significant abnormalities in the results of objective tests (e.g. laboratory variables, fetal ultrasound abnormalities) will also be recorded as AEs. If the results are not expected as part of disease or IMP, these will also be recorded as unexpected. All AEs will be recorded with clinical symptoms and accompanied with a simple, brief description of the event, including dates as appropriate.

All AEs will be captured up to 6 weeks postpartum.

Certain adverse events are considered to constitute expected pregnancy-related symptoms/clinical signs that will not be recorded in the CRF, nor in the AE log.

3. Discussion

3.1. Assessment of compliance

The percentage of noncompliance acceptable for participant to continue on the trial is as follows: <80% compliance equates to participant withdrawal (this includes compliance with IMP and study procedures i.e. visit window, refusal of study specific assessments).

Percentage of IMP compliance acceptable for participant to continue on the trial is 80% or greater.

Noncompliance with the protocol study procedures will be documented by the investigator and reported to the Sponsor as agreed.

Persistent noncompliance may lead the participant to be withdrawn from the study.

3.2. Limitations

As described above regarding participant compliance, if a participant has not taken at least 80% of the trial medication or not attended at least 80% of the scheduled visits, they will be excluded from the trial.

Trial insurance

Royal College of Surgeons in Ireland.

Data monitor

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RCSI.

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Trial status

This is an ongoing study currently.

Protocol version 1–15/3/18.

Date of planned recruitment – 2/1/2019.

Date of recruitment completion – 2/1/2022 approximately.

Ethical approval granted by National Maternity Hospital Ethics Committee on June 18, 2018.

HPRA approval granted pending SSA's.

Ethical approval

Approved by the National Maternity Hospital Ethics Committee June 18, 2018, Dublin, Ireland.

Consent to participate

Participants will provide written consent to participate in the trial, none have been recruited yet.

Consent for publication

Not applicable.

Availability of data and material

Full trial protocol available at request of Principal Investigator Prof Fionnuala Breathnach, fbreathnach@rcsi.ie.

Trial data will be made available on request once the trial commences and data is generated.

Competing interests

The authors declare that they have no competing interests.

Funding

Funding was granted by the Health research Board (HRB) 1/9/2017 (DIFA-2017-026). The trial was peer-reviewed by the funding body. The funder has no further role in the study.

Author's contributions

Conception of this work by CF, based on the trial designed by FB, PD, ET, EF, MH, SD, MOR, FD, GG, JS and VC.

Trial sponsor

Royal College of Surgeons in Ireland, 123 St Stephen's Green, Dublin

2.

Role of Sponsor and Funders in data collection and analysis:

Neither the sponsor nor the funder had any role in trial design. Neither the sponsor or the funder will have any role in: data collection; data analysis; data interpretation; report writing; or the decision to submit the manuscript for publication.

Trial registration

EudraCT Number 2018-000770-29, Registered February 21, 2018.

Acknowledgements

The above authors for contributing to the complete protocol submission to the HPRAs.

List of abbreviations

DM	Diabetes Mellitus
DSMB	Data Safety Monitoring Board
eCRF	electronic Case Report Form
EudraCT	European Clinical Trials Database
HPRAs	Health Product Regulatory Authority
HSE	Health Services Executive
ITT	Intention To Treat
NICE	National Institute for Health and Care Excellence
NICU	Neonatal Intensive Care Unit
PI	Principal Investigator
SSA	Site Specific Assessment

APPENDICES.

1. Participant Consent Form

2. Participant Information Leaflet

3. GP Letter

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.conctc.2019.100465>.

References

- [1] P.R. Garner, M.E. D'Alton, D.K. Dudley, P. Huard, M. Hardie, Preeclampsia in diabetic pregnancies, *Am. J. Obstet. Gynecol.* 163 (1990) 505–508.
- [2] B.M. Sibai, S.N. Caritis, E. Thom, et al., Prevention of preeclampsia with low-dose aspirin in healthy, nulliparous pregnant women, *N. Engl. J. Med.* 329 (1993) 1213–1218.
- [3] E. Schiff, E. Peleg, M. Goldenberg, et al., The use of aspirin to prevent pregnancy-induced hypertension and lower the ratio of thromboxane A2 to prostacyclin in relatively high risk pregnancies, *N. Engl. J. Med.* 321 (1989) 351–356.
- [4] M. Beaufils, S. Uzan, R. Donsimoni, J.C. Colau, Prevention of pre-eclampsia by early antiplatelet therapy, *Lancet* 1 (1985) 840–842.
- [5] H.C.S. Wallenburg, G.A. Dekker, J.W. Makovitz, P. Rotmans, Low-dose aspirin prevents pregnancy-induced hypertension and pre-eclampsia in angiotensin-sensitive primigravidae, *Lancet* 1 (1986) 1–3.
- [6] J.C. Hauth, R.L. Goldenberg, C.R. Parker Jr., et al., Low-dose aspirin therapy to prevent preeclampsia, *Am. J. Obstet. Gynecol.* 168 (1993) 1083–1091.
- [7] B. Sibai, G. Dekker, M. Kupferminc, Preeclampsia. *Lancet* 365 (2005) 785–799.
- [8] CLASP (Collaborative Low-dose Aspirin Study in Pregnancy), Collaborative Group. CLASP: a randomised trial of low-dose aspirin for the prevention and treatment of pre-eclampsia among 9364 pregnant women, *Lancet* 343 (1994) 619–629.
- [9] ECPPA (Estudo Colaborativo para Prevenção da Pré-eclampsia com Aspirina), Collaborative Group. ECPPA: randomised trial of low dose aspirin for the prevention of maternal and fetal complications in high risk pregnant women, *Br J Obstet Gynecol* 103 (1996) 39–47.
- [10] L.M. Askie, L. Duley, D.J. Henderson-Smart, et al., Antiplatelet agents for prevention of preeclampsia: a metaanalysis of individual patient data, *Lancet* 369 (2007) 1791–1798.
- [11] D. Kenny, et al., A National evaluation of the aspirin response, *Ir. J. Med. Sci.* 182 (Suppl 8) (2013) S359–S392.