

Joana Maria Sousa Nunes

**Monochorionicity in twin pregnancies, crown-rump length
and birthweight discordancy: the trio of influence**

Monocorionicidade em gravidezes gemelares, comprimento
craniocaudal e discordância de peso fetal: o trio de influência

março, 2017

Joana Maria Sousa Nunes

Monochorionicity in twin pregnancies, crown-rump length and
birthweight discordancy: the trio of influence

Monocorionicidade em gravidezes gemelares, comprimento
craniocaudal e discordância de peso fetal: o trio de influência

Mestrado Integrado em Medicina

Área: Obstetrícia

Tipologia: Dissertação

Trabalho efetuado sob a Orientação de:

Doutora Alexandra Matias Pereira da Cunha Coelho de Macedo

Trabalho organizado de acordo com as normas da revista:

Journal of Perinatal Medicine

março, 2017

Eu, Jana Maria Sousa Nunes, abaixo assinado, nº mecanográfico 201103627, estudante do 6º ano do Ciclo de Estudos Integrado em Medicina, na Faculdade de Medicina da Universidade do Porto, declaro ter atuado com absoluta integridade na elaboração deste projeto de opção.

Neste sentido, confirmo que **NÃO** incorri em plágio (ato pelo qual um indivíduo, mesmo por omissão, assume a autoria de um determinado trabalho intelectual, ou partes dele). Mais declaro que todas as frases que retirei de trabalhos anteriores pertencentes a outros autores, foram referenciadas, ou redigidas com novas palavras, tendo colocado, neste caso, a citação da fonte bibliográfica.

Faculdade de Medicina da Universidade do Porto, 15/03/2017

Assinatura conforme cartão de identificação:

Jana Maria Sousa Nunes

NOME

Joana Maria Sousa Nunes

NÚMERO DE ESTUDANTE

201103627

DATA DE CONCLUSÃO

15/03/2017

DESIGNAÇÃO DA ÁREA DO PROJECTO

Obstetrícia

TÍTULO DISSERTAÇÃO/MONOGRAFIA (riscar o que não interessa)

Monochorionicity in twin pregnancies, crown-rump length and birthweight discordancy: the trio of influence

ORIENTADOR

Doutora Alexandra Matias Pereira da Cunha Coelho de Macedo

COORDENADOR (se aplicável)

ASSINALE APENAS UMA DAS OPÇÕES:

É AUTORIZADA A REPRODUÇÃO INTEGRAL DESTA OBRA APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☒
É AUTORIZADA A REPRODUÇÃO PARCIAL DESTA OBRA (INDICAR, CASO TAL SEJA NECESSÁRIO, Nº MÁXIMO DE PÁGINAS, ILUSTRAÇÕES, GRÁFICOS, ETC.) APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☐
DE ACORDO COM A LEGISLAÇÃO EM VIGOR, (INDICAR, CASO TAL SEJA NECESSÁRIO, Nº MÁXIMO DE PÁGINAS, ILUSTRAÇÕES, GRÁFICOS, ETC.) NÃO É PERMITIDA A REPRODUÇÃO DE QUALQUER PARTE DESTA OBRA.	☐

Faculdade de Medicina da Universidade do Porto, 15/03/2017

Assinatura conforme cartão de identificação: Joana Maria Sousa Nunes

Agradecimentos

Dedico esta tese de mestrado a todos aqueles que contribuíram para que o meu trabalho desse frutos e permitisse o desenvolvimento desta dissertação. A todos, o meu sincero agradecimento pessoal.

À Professora Doutora Alexandra Matias, minha orientadora, por todas as recomendações, sabedoria, simpatia e proatividade, com que sempre orientou o meu trabalho.

Ao Doutor Isaac Blickstein e ao Professor Doutor Mário Sousa, pelos ensinamentos, dedicação e experiência pessoal, com os quais me permitiram fortalecer esta dissertação.

A todo o corpo docente, departamentos e serviços deste hospital universitário, no qual pude crescer ao longo destes 6 anos de curso de Medicina.

Aos meus pais e família, por todo o amor incondicional, estímulo, apoio e ensinamentos, impossíveis de serem descritos por palavras.

Ao meu namorado e amigos, pela união, cumplicidade e motivação, em todos os momentos.

Monochorionicity in twin pregnancies, crown-rump length and birthweight discordancy: the trio of influence

Joana Nunes, Degree in Basic Health Sciences, Master Degree in Medicine, Faculty of Medicine, University of Porto

Alexandra Matias, MD PhD, Senior Consultant of OB/GYN, S. João, Faculty of Medicine, University of Porto

Isaac Blickstein, MD PhD, Senior Consultant of OB/GYN, Kaplan Medical Center, Rehovot, Hadassah-Hebrew University School of Medicine, Jerusalem

Mário Sousa, MD PhD Pos-Doctorat, Cathedratric/Full Professor, ICBAS - St António General Hospital, University of Porto

CORRESPONDENCE:

Joana Maria Sousa Nunes

Praceta Ferreira de Castro, nº39, 4º dto., 4425-082, Águas Santas, Maia, Portugal

917309410

mimed11103@med.up.pt

ACKNOWLEDGEMENTS

We would like to thank Nuno Montenegro, MD PhD, Senior Consultant in OB/GYN, S. João, Faculty of Medicine, University of Porto, for taking interest in this scientific dissertation.

Monochorionicity in twin pregnancies, crown-rump length and birthweight discordancy: the trio of influence

Sousa Nunes, J; Blickstein, I; Sousa, M; Matias, A

Faculdade de Medicina da Universidade do Porto

Abstract

Objective

The purpose of this study was to analyze retrospectively the influence of chorionicity in the biometric parameters crown-rump length (CRL) and birthweight (BW), as well as their association when inter-twin discordancy occurs.

Material and Methods

The literature review (2000-2016) was based on 34 final articles, 33 from PubMed and 1 from Scopus. The statistical analysis was based on the twin pregnancy database of Centro Hospitalar S. João (2010-2015), including 66 monochorionic gestations (MC) and 177 dichorionic gestations (DC).

Results

There wasn't a statistically significant difference in BW (p value=0,09) and in BW discordancy (BWD) (p value=0,06) between MC and DC, as for CRL (p value=0,48) and CRL discordancy (CRLD) (p value=0,74). Among all gestations, CRLD and BWD were associated by the regression line $y = 0,8864x + 0,0743$, with $r^2 = 0,1599$. 7,58% (MC) and 13,56% (DC) of CRLD were $\geq 10\%$ and 16,67% (MC) and 31,64% (DC) of BWD were $\geq 15\%$.

Conclusion

Slightly there was not a statistically significant influence of chorionicity in BW and BWD, in comparison with its evidently irrelevant influence in CRL and CRLD. BWD was explained in 16% by CRLD. A superior clinically relevant discordancy in CRL and BW was verified in DC.

Keywords

fetal growth; growth discordancy; crown-rump length; birthweight; chorionicity; twins

Introduction

Twinning is increasing over time and many researchers have stated that multiple pregnancies are at a higher risk of mortality and morbidity than singletons [1,4,5,6,9]. According to the classification of twin pregnancies, no matter how many fetuses we are dealing with (zygosity), what really counts for perinatal outcome of twin pregnancies is the type of placentation (chorionicity) [1,2,4,5,6,10,23]. In the literature, only a single author favors a contrasting opinion [7]. Monochorionic twin gestations (MC) present a less favorable scenario, causing some well-studied consequences [8,23,27,29,31]. Furthermore, the importance of chorionicity on twin growth patterns is well established, being MC more frequently related to growth restriction, low birthweight (BW) and birthweight discordancy (BWD) [20-26, 28-31]. BWD affects up to 20% of MC and only 8% of dichorionic twin gestations (DC) [28], being unequal placental sharing the major contributor, according to Lewi and Blickstein [21]. This condition can be divided into three categories: <15% (concordant), 15-25% (mildly discordant) and >25% (severely discordant) growth [25,30]. These chorionicity-dependent abnormal growth patterns cause worse outcomes since the obstetric management is not well established yet [31]. The use of first trimester transvaginal ultrasonography is therefore mandatory in order to obtain an early accurate determination of multiple gestations, their chorionicity and zygosity, as well as to calculate some important biometric parameters as crown-rump length (CRL) and its inter-twin discordancy [1,9]. Some authors have analyzed this inter-twin CRL discordancy ($\geq 10\%$) as a cause of an increased risk of fetal anomalies and growth restriction, affecting BW in the long run [32]. Contrarily, other studies classified the CRL discordancy as a poor predictor of adverse outcome [33, 34]. The purpose of this study was to analyze retrospectively the influence of the chorionicity in two biometric parameters, crown-rump length (CRL) and birthweight (BW), as well as to establish the association of both when there is inter-twin discordancy.

Material and Methods

A search of the available literature from 2000 to 2016 was performed in PubMed, Scopus and Google Scholar using the following queries: “((twins[MeSH Terms] OR dizygotic twins[MeSH Terms] OR monozygotic twins[MeSH Terms]) AND (placentation[MeSH Terms] OR chorion[MeSH Terms]) AND (embryonic and fetal development[MeSH Terms] OR biometry[MeSH Terms] OR fetal growth[MeSH Terms])) AND (“2000”[Date - Publication] : “3000”[Date - Publication])) AND “english”[Language]”, used in Pubmed, where 94 articles were found, and “TITLE-ABS-KEY (((twins OR dizygotic twins OR monozygotic twins) AND (placentation OR chorion) AND (embryonic AND fetal development OR biometry OR fetal growth))) AND SUBJAREA (mult OR medi OR nurs OR vete OR dent OR heal) AND PUBYEAR > 1999 AND (LIMIT-TO (LANGUAGE , “English”)) AND (LIMIT-TO (SUBJAREA , “MEDI”))”, used in Scopus, where 16 articles were considered. The first query was used in Google Scholar database, which identified some articles already found in the previous databases. The 110 first articles were afterwards analysed according to their title and abstract, as well as to some established exclusion and inclusion criteria, reading afterwards the most relevant ones integrally. The exclusion criteria were multiple pregnancies which were not twin pregnancies; molecular, histologic and immunologic studies; presence of twin-to-twin transfusion syndrome or pathologic gestations; studies whose analysis did not included different chorionicity between the analysed groups; studies that analyzed parameters other than embryonic and fetal biometric, development and outcome ones; case reports; non-human gestational studies. The inclusion criteria were twin pregnancies; human gestations; healthy gestations; comparison of biometric, development and outcome parameters according to chorionicity; studies since 2000 to 2016. After this electronic and manual search and selection, the following review was based on 34 articles, 33 from PubMed and 1 from Scopus.

The statistical analysis was based on the twin pregnancy database of Centro Hospitalar S. João of the last 5 years (2010-2015). We considered a total of 706 fetuses. From those, we enclosed 486 fetuses, 132 from 66 MC (each one

with fetus 1 and fetus 2) and 354 from 177 DC (each one with fetus 1 and fetus 2), being excluded fetuses from trichorionic gestations or from those with inconclusive chorionicity. In this database, we considered two biometric parameters: CRL, evaluated in the 1st trimester obstetric ultrasonography, as well as BW, verified right after labor. The defined objectives for the statistical analysis were: 1st – compare the two parameters of all fetuses according to chorionicity, as well as between fetuses 1 according to chorionicity and also between fetuses 2 according to chorionicity; 2nd - determine the association between CRLD and BWD and analyze the regression line of their association graph. The discordancy of each parameter was calculated by using the ratio between the difference of the measurements of each fetus of the same gestation and the larger measurement between them; 3rd – once, according to the literature, the CRLD was considered of major importance if it was equal or above 10% and, in case of BWD, if it was equal or above 15%, the discordancy of both parameters was analyzed for both MC and DC. The statistical analysis was done using IBM SPSS Statistics 23.

The present investigation was approved by the hospital's ethics committee and authorized by the Centro Hospitalar S. João Board of Directors (Annexes 3).

Results

Concerning the 1st statistical objective, we analyzed the data of the total number of fetuses, fetuses 1 and fetuses 2, concerning CRL and BW according to their chorionicity. Regarding the influence of chorionicity type among all fetuses, we obtained, with the parametric T-test, p value=0,48 ($>0,05$), for CRL parameter, and p value=0,09 ($>0,05$), for BW parameter. Concerning the influence of chorionicity for fetuses 1, we obtained, with the parametric T-test, a p value=0,68 ($>0,05$), for the CRL parameter, and p value=0,12 ($>0,05$), for the BW parameter. In what concerns the influence of chorionicity for fetuses 2, we obtained, with the parametric T-test, p value=0,56 ($>0,05$), for the CRL parameter, and p value=0,40 ($>0,05$), for the BW parameter (Tables 1 and 2). Concerning the 2nd statistical objective, we determined the association between CRL discordancy and BW discordancy and analyzed the regression line of their association graph. The discordancy of each parameter was calculated in percentage by using the ratio between the difference of the measurements of each fetus of the same gestation and the larger measurement between them. The results obtained can be seen in Graph 1 (Correlation between CRL discordancy and BW discordancy, among all gestations), in which the regression line is defined by $\text{BW discordancy} = 0,8864 \times \text{CRL discordancy} + 0,0743$, with $r^2=0,1599$, being r^2 (coefficient of determination) the variation of BW discordancy explained by CRL discordancy. In Graph 2, the correlation between CRL discordancy and BW discordancy among MC is displayed, in which the regression line is defined by $\text{BW discordancy} = 0,7312 \times \text{CRL discordancy} + 0,0623$, with $r^2=0,1763$. In Graph 3, the correlation between CRL discordancy and BW discordancy among DC can be seen, in which the regression line is defined by $\text{BW discordancy} = 0,9438 \times \text{CRL discordancy} + 0,0787$, with $r^2=0,1591$.

Concerning the 3rd statistical objective, CRL and BW discordancies for both monochorionic and dichorionic gestations was analysed. According to the literature, discordancy in CRL equal or above 10% and, in BW, equal or above 15% was considered of clinical importance. The results achieved showed that 7.58% of MC showed a CRLD of at least 10%, against 13.56% among DC. It

was also verified that 16.67% of MC had a BW discordancy of at least 15%, against 31.64% among DC. We also analysed the influence of chorionicity in CRL discordancy (Table 3) and BW discordancy (Table 4), and obtained p value=0.74 (>0.05) and p value=0.06 (>0.05), respectively.

Conclusion

No statistically significant difference for CRL and BW according to chorionicity was verified, but a borderline non-statistically difference was observed for BW, comparing to CRL in which the value itself is completely not statistically different. This can be explained by the early development phase in which the CRL measurement is performed, and therefore the influence of chorionicity in fetal growth may not be noticeable until later in pregnancy when the BW is estimated. Maybe in future studies with a larger sample this influence of chorionicity in BW will be more apparent.

Among all gestations, nearly 16% of the BW discordancy is explained by CRL discordancy. Among monochorionic gestations, nearly 18% of the BW discordancy is explained by the CRL discordancy, not very different from what happens in dichorionic gestations in which nearly 16% of the BW discordancy is explained by the CRL discordancy. It would be interesting in future studies to clarify the other determinants that explain the BWD other than CRLD.

There is a higher percentage of discordancy in CRL equal or above 10% in DC (13.56%) than in MC (7.58%). Regarding the BW discordancy, there is also a greater percentage of major and clinical important discordancy of at least 15% in DC (31.54%) than in MC (16.67%). This can be explained by the more independent growth of the two fetuses when each one has its own placenta (dichorionic gestations) than when they share the same territory (monochorionic gestations).

The influence of chorionicity type was not statistically significant in BW discordancy and CRL discordancy, but far more evidently non-statistically different in this last parameter, which can also be explained by the early developmental phase in which CRL is measured. The fetal growth progression and the later phases of development will possibly allow for more measurement manifestations of the more independent and diverse growth of the two fetuses when there are two placentas available (dichorionic gestations), which could be more concretely understood by a larger study sample. Another possible limitation of the results is the interobserver variability once the CRL and BW measurements were done by different health professionals.

Conflict of interests

The authors have no conflict of interests to report.

References

1. Constantine S, Wilkinson C. Double trouble: The importance of reporting chorionicity and amnionicity in twin pregnancy ultrasound reports. *J Med Imaging Radiat Oncol*. 2015 Feb;59(1):66-9..
2. Mihailidis S, Bockmann M, McConnell E, Hughes T, van Beijsterveldt TC, Boomsma DI, et al. The Influence of Chorion Type on Health Measures at Birth and Dental Development in Australian and Dutch Twins: A Comparative Study. *Twin Res Hum Genet*. 2015 Aug;18(4):368-74.
3. Kyono K. The Precise Timing of Embryo Splitting for Monozygotic Dichorionic Diamniotic Twins: When Does Embryo Splitting for Monozygotic Dichorionic Diamniotic Twins Occur? Evidence for Splitting at the Morula/Blastocyst Stage From Studies of In Vitro Fertilization. *Twin Res Hum Genet*. 2013 Aug;16(4):827-32.
4. Farah N, Hogan J, Johnson S, Stuart B, Daly S. Prospective risk of fetal death in uncomplicated monochorionic twins. *Acta Obstet Gynecol Scand*. 2012 Mar;91(3):382-5.
5. Oldenburg A, Rode L, Bødker B, Ersbak V, Holmskov A, Jørgensen FS, et al. Influence of chorionicity on perinatal outcome in a large cohort of Danish twin pregnancies. *Ultrasound Obstet Gynecol*. 2012 Jan;39(1):69-74.
6. Glinianaia SV1, Obeyesekera MA, Sturgiss S, Bell R. Stillbirth and neonatal mortality in monochorionic and dichorionic twins: a population-based study. *Hum Reprod*. 2011 Sep;26(9):2549-57.
7. Lee KA, Oh KJ, Lee SM, Kim A, Jun JK. The Frequency and Clinical Significance of Twin Gestations According to Zygosity and Chorionicity. *Twin Res Hum Genet*. 2010 Dec;13(6):609-19.
8. Ortibus E, Lopriore E, Deprest J, Vandenbussche FP, Walther FJ, Diemert A, et al. The pregnancy and long-term neurodevelopmental outcome of monochorionic diamniotic twin gestations: a multicenter prospective cohort study from the first trimester onward. *Am J Obstet Gynecol*. 2009 May;200(5):494.e1-8.
9. Sherer DM. Is less intensive fetal surveillance of dichorionic twin gestations justified? *Ultrasound Obstet Gynecol*. 2000 Mar;15(3):167-73.

10. Carroll SG, Tyfield L, Reeve L, Porter H, Soothill P, Kyle PM. Is zygosity or chorionicity the main determinant of fetal outcome in twin pregnancies? *Am J Obstet Gynecol.* 2005 Sep;193(3 Pt 1):757-61.
11. Papageorgiou AT, Bakoulas V, Sebire NJ, Nicolaides KH. Intrauterine growth in multiple pregnancies in relation to fetal number, chorionicity and gestational age. *Ultrasound Obstet Gynecol.* 2008 Dec;32(7):890-3.
12. Cleary-Goldman J, D'Alton ME. Growth Abnormalities and Multiple Gestations. *Semin Perinatol.* 2008 Jun;32(3):206-12.
13. Hur YM, Shin JS Effects of Chorion Type on Genetic and Environmental Influences on Height, Weight, and Body Mass Index in South Korean Young Twins. *Twin Res Hum Genet.* 2008 Feb;11(1):63-9.
14. Cordero L, Franco A, Joy SD. Monochorionic monoamniotic twins: neonatal outcome. *J Perinatol.* 2006 Mar;26(3):170-5.
15. Cordero L, Franco A, Joy SD, O'shaughnessy RW. Monochorionic Diamniotic Infants Without Twin-to-Twin Transfusion Syndrome. *J Perinatol.* 2005 Dec;25(12):753-8.
16. Loos RJ, Derom C, Derom R, Vlietinck R. Determinants of birthweight and intrauterine growth in liveborn twins. *Paediatr Perinat Epidemiol.* 2005 Jan;19 Suppl 1:15-22.
17. González-Quintero VH, Luke B, O'sullivan MJ, Misiunas R, Anderson E, Nugent C, et al. Antenatal factors associated with significant birth weight discordancy in twin gestations. *Am J Obstet Gynecol.* 2003 Sep;189(3):813-7.
18. Senoo M, Okamura K, Murotsuki J, Yaegashi N, Uehara S, Yajima A. Growth Pattern of Twins of Different Chorionicity Evaluated by Sonographic Biometry. *Obstet Gynecol.* 2000 May;95(5):656-61.
19. Araujo Júnior E, Ruano R, Javadian P, Martins WP, Elito J Jr, Pires CR, et al. Reference charts for fetal biometric parameters in twin pregnancies according to chorionicity. *Prenat Diagn.* 2014 Apr;34(4):382-8.
20. Blickstein I, Keith LG. Neonatal mortality rates among growth-discordant twins, classified according to the birth weight of the smaller twin. *Am J Obstet Gynecol.* 2004 Jan;190(1):170-4.

21. Lewi L, Cannie M, Blickstein I, Jani J, Huber A, Lewi P, et al. Placental sharing, birthweight discordance, and vascular anastomoses in monochorionic diamniotic twin placentas. *Am J Obstet Gynecol*. 2007 Dec;197(6):587.e1-8.
22. Simoes T, Julio C, Cordeiro A, Cohen A, Silva A, Blickstein I. Abdominal circumference ratio for the diagnosis of intertwin birth weight discordance. *J Perinat Med*. 2011 Jan;39(1):43-6.
23. Blickstein I, Mincha S, D Goldman R, A Machin G, G Keith L. The Northwestern twin chorionicity study testing the 'placental crowding' hypothesis. *J Perinat Med*. 2006;34(2):158-61.
24. Reberdao MA, Martins L, Torgal M, Viana R, Seminova T, Blickstein I. The source of error in the estimation of intertwin birth weight discordance. *J Perinat Med*. 2010 Nov;38(6):671-4.
25. Blickstein I, Shoham-Schwartz Z, Lancet M, Borenstein R. Characterization of the growth-discordant twin. *Obstet Gynecol*. 1987 Jul;70(1):11-5.
26. Blickstein I, Goldman RD, Mazkereth R. Adaptive Growth Restriction as a Pattern of Birth Weight Discordance in Twin Gestations. *Obstet Gynecol*. 2000 Dec;96(6):986-90.
27. Hack KE, van Gemert MJ, Lopriore E, Schaap AH, Eggink AJ, Elias SG, et al. Placental Characteristics of Monoamniotic Twin Pregnancies in Relation to Perinatal Outcome. *Obstet Gynecol*. 2000 Dec;96(6):986-90.
28. Lopriore E1, Pasman SA, Klumper FJ, Middeldorp JM, Walther FJ, Oepkes D. Placental characteristics in growth-discordant monochorionic twins: a matched case-control study. *Placenta*. 2012 Mar;33(3):171-4.
29. Simões T, Cordeiro A, Júlio C, Reis J, Dias E, Blickstein I. Perinatal Outcome and Change in Body Mass Index in Mothers of Dichorionic Twins A Longitudinal Cohort Study. *Twin Res Hum Genet*. 2008 Apr;11(2):219-23.
30. Blickstein I, Kalish RB. Birthweight Discordance in Multiple Pregnancy. *Twin Res*. 2003 Dec;6(6):526-31.
31. Lopriore E, Sluimers C, Pasman SA, Middeldorp JM, Oepkes D, Walther FJ. Neonatal Morbidity in Growth-Discordant Monochorionic Twins: Comparison Between the Larger and the Smaller Twin. *Twin Res Hum Genet*. 2012 Aug;15(4):541-6.

32. Grande M, Goncé A, Stergiotou I, Bennasar M, Borrell A. Intertwin crown-rump length discordance in the prediction of fetal anomalies, fetal loss and adverse perinatal outcome. *J Matern Fetal Neonatal Med.* 2016 Sep;29(17):2883-8.
33. Ben-Ami I, Sheena L, Svirsky R, Odeh M, Rosen H, Melcer Y, et al. The association of crown-rump length discrepancy with birthweight discordance in spontaneous versus assisted conception dichorionic twins. *Prenat Diagn.* 2014 Aug;34(8):748-52.
34. D'Antonio F, Khalil A, Pagani G, Papageorgiou AT, Bhide A, Thilaganathan B. Crown-rump length discordance and adverse perinatal outcome in twin pregnancies: systematic review and meta-analysis. *Ultrasound Obstet Gynecol.* 2014 Aug;44(2):138-46.

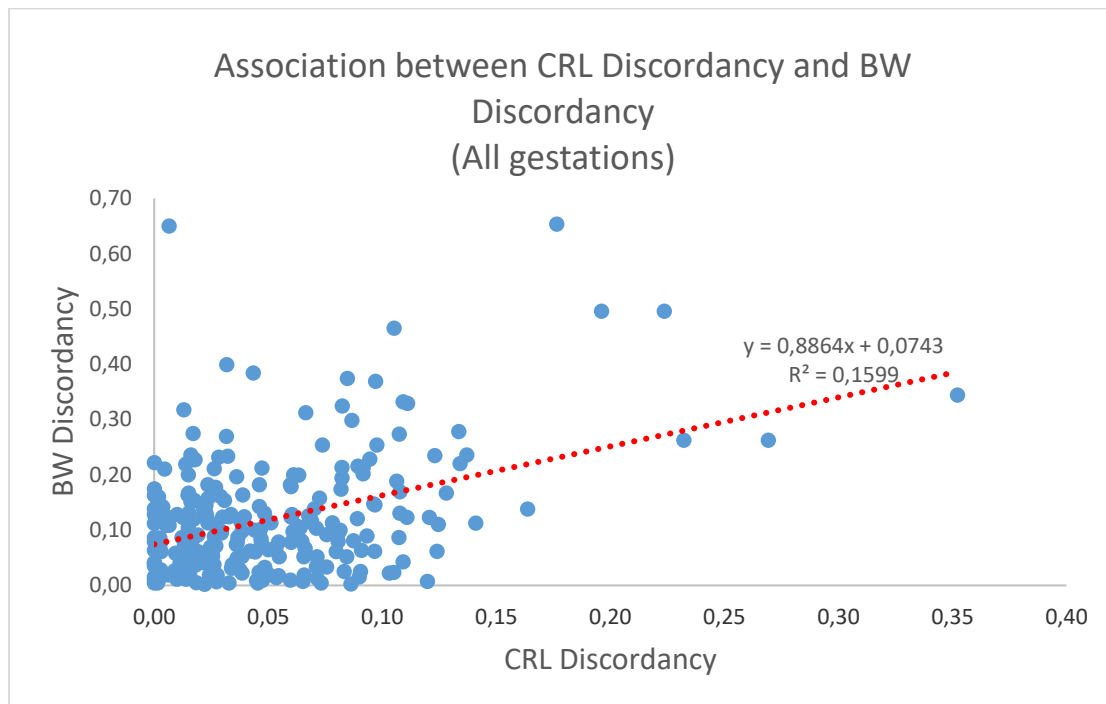
Annexes 1

Tables and graphs

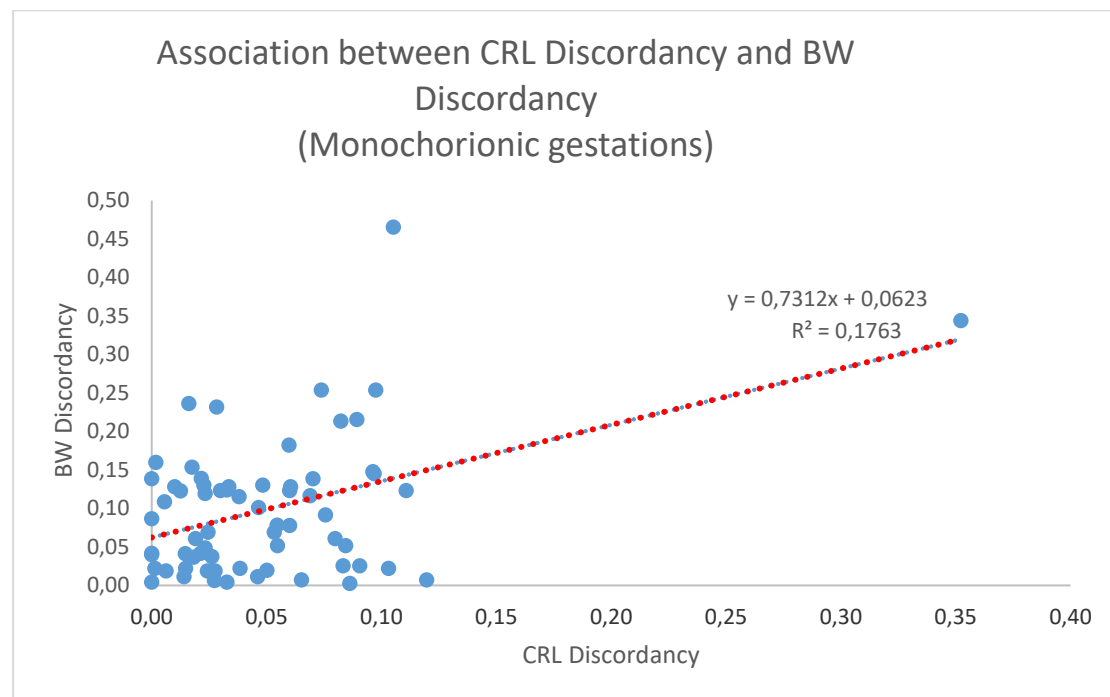
Table 1. Influence of chorionicity in crown-rump length (CRL) (mm)			
	Monochorionic	Dichorionic	p
All fetuses	62,01 ± 14,12	61,07 ± 10,03	0,48
Fetuses 1	62,08 ± 13,76	61,31 ± 9,92	0,68
Fetuses 2	61,94 ± 14,59	60,82 ± 10,17	0,56

Table 2. Influence of chorionicity in birthweight (BW) (g)			
	Monochorionic	Dichorionic	p
All fetuses	2150,87 ± 554,75	2244,50 ± 536,81	0,09
Fetuses 1	2168,26 ± 591,43	2290,17 ± 522,44	0,12
Fetuses 2	2133,48 ± 519,44	2198,84 ± 548,47	0,40

Graph 1. Correlation between crown-rump length discordancy (CRLD) and birthweight discordancy (BWD), among all gestations.



Graph 2. Correlation between crown-rump length discordancy (CRLD) and birthweight discordancy (BWD), among monochorionic gestations.



Graph 3. Correlation between crown-rump length discordancy (CRLD) and birthweight discordancy (BWD), among dichorionic gestations.

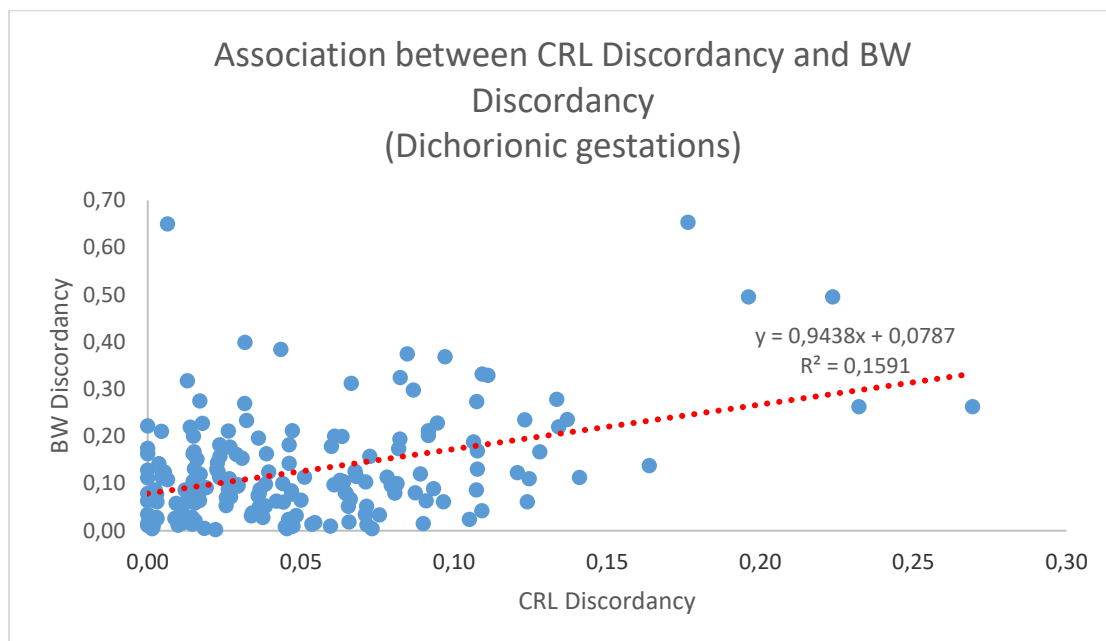


Table 3. Influence of chorionicity type in crown-rump length discordancy (CRLD)			
	Monochorionic	Dichorionic	P
All gestations	0,049 ± 0,050	0,051 ± 0,047	0,74

Table 4. Influence of chorionicity in birthweight discordancy (BWD)			
	Monochorionic	Dichorionic	p
All gestations	0,098 ± 0,088	0,127 ± 0,112	0,06

Annexes 2

Instructions for authors of Journal of Perinatal Medicine

Scope of the journal

- **Journal of Perinatal Medicine** publishes original papers and reviews on all aspects of obstetrical and neonatal research and provides rapid publication for all items of articles.
- **Review articles** providing a coverage of theoretical and practical points of view in a particular field: Manuscript: length according to previous arrangement. References should be limited to max. 50 citations.
- **Original contributions** reporting on new results, particularly from the clinical and experimental areas. Manuscript: approx. 8 pages. Abstract: approx. 200 words. References should be limited to max. 35 citations.
- **Short communications** – rapid publication of new/preliminary results. Manuscript: maximum 3 pages, 1 figure, 1 table. Abstract. References should be limited to max. 10 citations.
- **Opinion papers** – invited statements on themes of topical interest.
- **Technical notes** describing the characteristics of new instruments or methodological improvements. Manuscript: maximum 2 pages, 1 figure.
- **Letters of the Editors** – permitting exchange of views and information on controversial topics discussed at conferences and meetings, and comments on previously published material with absolute minimum delay. Manuscript: maximum 1 page.
- **WAPM-Newsletter** – Information of the World Association of Perinatal Medicine.

We ask for your understanding that Case reports can no longer be considered in the Journal of Perinatal Medicine. However continuous readers' interest and significant relevance of case reports inspired the Editors and Publishers of the Journal of Perinatal Medicine to found a new journal named "Case Reports in Perinatal Medicine" (please see <http://www.degruyter.com/view/j/crpm>).

Review of manuscripts and speed of publication

All contributions submitted for publication are critically reviewed by at least two renowned experts in the field in order to ensure constant high quality of the journal. If both approve the paper it will be accepted for publication and forwarded to the Associate Editors for further editorial processing.

Abstracts of meetings can be published at page charges (estimates are available on request).

Submission of Manuscripts

Please submit original manuscripts on-line at:

<http://mc.manuscriptcentral.com/jpm>

For further information please visit our website:

www.degruyter.de/journals/jpm

Direct all correspondence to:

Ms. Ingrid Gritsch

Editorial Office Journal of Perinatal Medicine

Walter de Gruyter GmbH

Genthiner Str. 13

10785 Berlin/Germany

Fax: +49-30-26005-298

Tel.: +49-30-26005-245

E-mail: JPM.editorial@degruyter.com

Authors are encouraged to recommend competent experts for reviewing in a separate cover letter.

Guidelines for preparation of manuscripts

Terminology of papers should be clearly understandable even to nontheorists. Manuscripts must be written in clear and concise English and should be regarded as final texts. Illustrations must be submitted in original quality. No changes may be made at the proof stage other than correction of printer's errors.

Language of publication

All articles appear in English/American.

Exclusive publication

Submission of a manuscript to *Journal of Perinatal Medicine* implies that the work described has not been published before and is not under consideration for publication elsewhere. Once the manuscript is accepted, it must not be published elsewhere without the consent of the copyright holders.

The Editor must reserve the right to make changes in the layout of individual parts of the manuscript in order to achieve unity and clarity.

• Abstract

An abstract of no more than 200 words should be provided for all types of contributions. It would state the aims, results, and any conclusions drawn.

• Keywords

Up to ten keywords should in alphabetical order be provided on a separate sheet. If possible the keywords should be taken from the Medical Subject Headings of Index Medicus.

• Figures

A reference to each figure is to be given in the text, e.g. (Figure 9). A caption should be provided for each figure in a list of captions.

Authors are encouraged to submit illustrations in color if necessary for their scientific content. Publication of color figures is provided free of charge both in online and print editions.

• Tables

Tables and their captions should be also numbered in sequence with Arabic numerals (Table 1).

• Literature citations

Please note that the journal has changed its reference format to

Vancouver style; further instructions at

<http://www.lib.mcmaster.ca/tutorial/citing/vancouver.html>

A. Reference within text:

References should be expressed as follows: Either in numbers [in square brackets] pertaining to the respective papers within the reference list (a) or under the author's name followed by the respective number in the reference list (b).

a. "As several authors [4, 17, 21] have reported ..."

b. "As Smith [14] and Windus [21] have reported ..."

B. Reference list:

The reference list containing all authors mentioned in the text, should be arranged in the order of appearance and numbered accordingly. The original title of every paper must be given in full and in the original language; abbreviations of periodical names should conform to those used in Index Medicus, National Library of Medicine. The style and punctuation of references should follow the format illustrated by the following examples:

1. Standard journal article

List the first six authors followed by et al. Halpern SD, Ubel PA, Caplan AL. Solid-organ transplantation in HIV-infected patients. *N Engl J Med*. 2002;347:284-7.

2. Organization as author

Diabetes Prevention Program Research Group. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension*. 2002;40:679-86.

3. No author given

21st century heart solution may have a sting in the tail. *BMJ*. 2002;325:184.

4. Book: Personal author:

Carlson BM. Human embryology and developmental biology. 3rd ed. St. Louis: Mosby; 2004.

Brown AM, Stubbs DW, editors. Medical physiology. New York: Wiley; 1983.

5. Chapter in a book:

Meltzer PS, Kallioniemi A, Trent JM. Chromosome alterations in human solid tumors. In: Vogelstein B, Kinzler KW, editors. The genetic basis of human cancer. New York: McGraw-Hill; 2002. p. 93-113.

Conflict of interest: Authors are responsible for recognizing and disclosing financial and other conflicts of interest that might bias their work. This information must be included in each manuscript. Please declare any conflicts of interest, funding, employment, or leadership and honoraria in an appropriate Acknowledgement placed previous to the reference section.

Annexes 3

Opinion and approval of the Ethics Committee and authorization by the Centro Hospitalar S. João Board of Directors

Comissão de Ética para a Saúde do C.H.S.João e da FMUP

Parecer

Titulo do Projecto: Monochorionicity in twin pregnancies, crown-rump length and birthweight discordancy: the trio of influence

Nome do Investigador Principal: Joana Maria Sousa Nunes

Promotor do Estudo: NA

Serviço onde decorrerá o Estudo: Serviço de Ginecologia e Obstetria do Centro Hospitalar de S. João

Objectivo e Pertinência do Estudo: Com este projecto de investigação, pretende-se analisar retrospectivamente a influência da corionicidade nos parâmetros biométricos "comprimento cranio-caudal" e "peso ao nascimento", bem como a associação entre estes dois últimos na presença de uma discordância inter-gemelar, de acordo com a base de dados de gravidezes gemelares do CHSJ nos últimos 5 anos, comparando os resultados obtidos com as descobertas da literatura disponível de 2000 a 2016.

Trata-se, pois, de um estudo retrospectivo e o desenho que lhe é dedicado adequa-se aos objectivos pretendidos. O acesso aos processos clínicos será realizado através do Elo de ligação.

Benefício/risco: NA

Respeito pela liberdade e autonomia do sujeito de ensaio: NA

Confidencialidade dos dados: A confidencialidade da informação recolhida será suportada na anonimização dos dados.

Elo de ligação: Doutora Alexandra Matias (Serviço de Ginecologia)

Indemnização por danos: NA

Continuação do tratamento: NA

Propriedade dos dados: Os dados serão propriedade exclusiva do Promotor/Investigador, e estão-lhe referidos critérios de divulgação dos resultados a alcançar.

Curriculum do investigador: Adequado ao perfil da investigação.

Data previsível da conclusão do estudo: Junho 2017

Conclusão: Considerados os objectivos do estudo e a metodologia que lhe está prevista, proponho um parecer favorável à realização deste projecto de investigação na sua actual definição metodológica.

Porto e H.S.João, 2016-11-18


O relator
Doutor Filipe Almeida

7. SEGURO

- a. Este estudo/projecto de investigação prevê intervenção clínica que implique a existência de um seguro para os participantes?

SIM ☐ (Se sim, junte, por favor, cópia da Apólice de Seguro respectiva)

NÃO ☐

NÃO APLICÁVEL ☒

8. TERMO DE RESPONSABILIDADE

Eu, Joana Maria Sousa Nunes

abaixo-assinado, na qualidade de Investigador Principal, declaro por minha honra que as informações prestadas neste questionário são verdadeiras. Mais declaro que, durante o estudo, serão respeitadas as recomendações constantes da Declaração de Helsínquia (com as emendas de Tóquio 1975, Veneza 1983, Hong-Kong 1989, Somerset West 1996 e Edimburgo 2000) e da Organização Mundial da Saúde, no que se refere à experimentação que envolve seres humanos. Aceito, também, a recomendação da CES de que o recrutamento para este estudo se fará junto de doentes que não tenham participado em outro estudo no decurso do actual internamento ou da mesma consulta.

Porto, 28 / Setembro / 2016

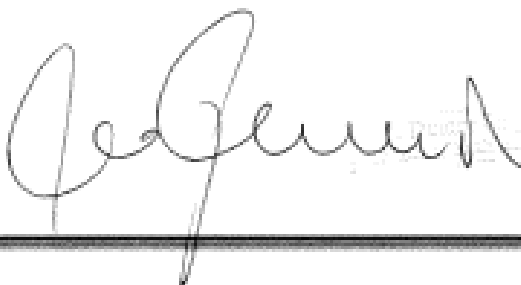
Joana Maria Sousa Nunes
O Investigador Principal

PARECER DA COMISSÃO DE ÉTICA PARA A SAÚDE DO CENTRO HOSPITALAR DE S. JOÃO

emitido na reunião plenária da CES

de
18, Novembro, 2016

A Comissão de Ética para a Saúde
APROVA por unanimidade o parecer do
Relator, pelo que nada tem a opor à
realização deste projecto de investigação.



Unidade de Investigação

Tomei conhecimento. Nada a opor.

02 de Janeiro de 2017

A Coordenadora da Unidade de Investigação

(Prof.ª Doutora Ana Azevedo)

DIRECÇÃO CLÍNICA

10 JAN 2017

Aprovado. Ao CA.

(Prof.ª Doutora Ana Azevedo)

AUTORIZADO

CLÍNICA DE ADMINISTRAÇÃO E HUMANIDADES 12 JAN 2017

Realizado em reunião de Administração

Presidente

Delegado

Delegado

Delegado

Exmo. Senhor

Presidente do Conselho de Administração do
Centro Hospitalar de S. João – EPE

Assunto: Pedido de autorização para realização de estudo/projecto de investigação

Nome do Investigador Principal: Joana Maria Sousa Nunes

Título do projecto de investigação: Monochorionicity in twin pregnancies, crown-rump length and birthweight discordancy: the trio of influence

Pretendendo realizar no(s) Serviço(s) de Ginecologia e Obstetria

do Centro Hospitalar de S. João – EPE o estudo/projecto de investigação em epígrafe, solicito a V. Exa., na qualidade de Investigador/Promotor, autorização para a sua efectivação.

Para o efeito, anexa toda a documentação referida no dossier da Comissão de Ética do Centro Hospitalar de S. João respeitante a estudos/projectos de investigação, à qual endereçou pedido de apreciação e parecer.

Com os melhores cumprimentos.

Porto, 28 / Setembro / 2016

O INVESTIGADOR/PROMOTOR

Joana Maria Sousa Nunes