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Review Article

Meta-analysis of reference values of haemostatic markers during pregnancy and childbirth

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ABSTRACT

Previously reported haemostatic reference intervals in normal pregnancy displayed considerable contradictions to establish convince gestational age-related haemostatic reference values. 30 clinical reports were recruited to collect and assemble existing clinical reports from the database D-dimer levels increased progressively with gestational ages and exceeded conventional value of 1 mg/L after 29–36 weeks, and reached a peak at 24 h postpartum with mean value of 6.44 mg/L [95% confidence interval (CI): 5.84 to 7.05] and returned to 0.79 mg/L (95% CI: 0.43 to 1.16) at 1–8 weeks postpartum. Analogously, the level of fibrinogen gradually increased throughout the pregnancy, and peaked at 48–72 h after birth, with mean value of 9.05 g/L (95% CI: 2.22 to 15.89) and then returned to 3.62 g/L (95% CI: 3.03 to 4.20) at 1–8 weeks postpartum. However, in the middle trimester, asynchronously prothromb in fragments 1 + 2 (F1+2) level elevated and reached a peak at 28–36 weeks with mean value of 3.05 nmol/L (95% CI: 2.41 to 3.70), and then decreased in the later trimester, and reached 1.92 nmol/L (95% CI: 0.58 to 3.27) at 48 –72 h post-partum, close to normal levels. Previously reported gestational age-related haemostatic reference intervals in pregnancy could not be used as a standard.

Introduction

The hypercoagulable state and high risk of venous thromboembolism (VTE) were relevant to pregnancy, partus and postpartum of pregnant women [1–3]. In clinical, D-dimer, fibrinogen, and prothrombin fragments 1 + 2 (F1+2) are mainly used to rule out of VTE in non-pregnant women [4,5]. However, these reference intervals are not applicable for pregnancy and postpartum.

Pregnancy is a special physiological state of balance. In order to adapt to pregnancy and delivery, coagulation and fibrinolytic activity increased and maintained at a high level. D-dimer is composed of fibrinolytic cross-linked fibrin, which increases the activity of secondary fibrinolytic. Fibrinogen is a kind of "central" protein in the coagulation system, which is directly involved in the coagulation process and increases obviously during pregnancy, making the blood in hypercoagulable state, which is helpful to hemostasis after delivery, but it is also easy to form thrombosis. F1+2 is the early product of clotting reaction of body and the active fragment of thrombin formation in the process of thrombin formation, which directly reflects the specific molecular marker of thrombinogen activation. Therefore, it has been an important clinical significance to find the special relationship between clotting markers and gestational age.

Currently, many studies has been reported that gestational age-specific haemostatic reference intervals were used for diagnosis thrombosis. However, there is a lack of consistency and even many contradictions in the data reported in these studies. For example, Kovac MK [6] and Kawaguch S [7] proposed that concentrations of D-dimer (1.0 or 2.0 mg/L) could be as threshold for helping diagnosis of VTE during pregnancy. However, Hedergran KK [8] denied this conclusion. Xu D [9] suggested that there were no significant

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differences of D-dimer levels between early and later pregnancy. On the contrary, Choi JW [10] demonstrated that D-dimer levels in later pregnancy were five-fold over than that in early pregnancy. During and after pregnancy, there is also much debate about the levels of fibrinogen and F1+2 [11–17].

The reference range of gestational coagulation markers has not been standardized, which can confuse clinical application and lead to clinical overdiagnosis and overtreatment. Inconsistencies may be due to the limited number of samples included in the study and the lack of consistency in blood samples taken during pregnancy.

According to the reference values of normal hemagglutination (D-dimer, fibrinogen and F1+2) during pregnancy and delivery, the arguments were clarified, the reference values of pregnancy markers were obtained, and the changes of various indexes with gestational age were observed. It is helpful for the diagnosis and study of venous thrombosis in pregnancy, even to avoid clinical misdiagnose and overtreatment.

Materials and methods

Participants

All pregnant women in the included studies had single birth, live birth, without complications during pregnancy. The age was above 18 years old.

Database and search strategy

Our study was conducted under the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA statement) [18]. PubMed, Medline, Embase databases, Cochrane Library electronic databases were searched for original studies, which reported normal pregnant women, and used ("pregnancy" OR "gestation" OR "postpartum" OR "partus") and ("D-dimer" OR "DD" OR "fibrinogen" OR "fib" OR "FBG" OR "fragments 1 + 2" OR "F1+2") as keywords.

Exclusion criteria

The exclusion criteria were: pregnancy complicated with VTE, diabetes, hypertension, preeclampsia, hematonosis, hereditary disease, and other diseases were excluded. Studies without gestational age groups were also excluded.

Study identification

Two authors (Juxian Tang and Yihui Lin) extracted the data from all eligible studies independently. If dispute was encountered, the third author (Duan Xiao) resolved in consultation. The following items were extracted: first author, publication year, country, location or data source, study design, sample size, mean age, group, reported outcomes and quality scores. All authors had no objection to the final result.

Quality assessment

The Newcastle-Ottawa Scale (NOS) guidelines [19] were used for studies quality assessment. Two authors (Juxian Tang and Huachao Mai) evaluated the quality of included studies. The studies were defined as two glasses [20]: high quality (6–9 scores) and poor quality (0–5 scores). If there were arguments about the scores of studies, the third author would participate to quality assessment.

Statistical analysis

The continuous data was pooled in our meta-analysis and the results were presented as mean value with 95% confidence interval (CI). We used a random-effect model to analyze all data, to draw cautious results. A p-value < 0.01 was regarded as significant differences, and all tests were two sided. All statistical analyses were performed using STATA version 12.0 (College Station, TX, USA).

Results

Description of studies

The study selection procedure was shown in Fig. 1. A total of 787 relevant studies were identified. 757 studies were excluded because of duplicates, not human studies, and case reports or drug intervention, pregnancy complications, without groups of gestational ages, lacking available data, no blood samples. 30 studies were ultimately pooled in the meta-analysis.

Characteristics of studies

The general characteristics of 30 studies, including 17522 normal pregnant women was shown in Table 1. The NOS score of all studies was over 5. The 30 studies were published between 1959 and 2016: 19 from Europe [6,8,14–17,21–32], 2 from America [33,34], 1 from Africa [13], and 8 from Asia [9,10,12,35–39], respectively. The age of patients was ranged from 18 to 44 years. All studies were non-randomized controlled or observational and reported gestational age-specified haemostatic reference intervals, including at least one of them (D-dimer, fibrinogen and F1+2).

Normal d-dimer reference values in pregnancy and post-partum

The concentration of D-dimer during pregnancy was reported in 23 studies, including 15514 normal pregnant women. Results showed that the mean value of 0.57 mg/L (95% CI: 0.43 to 0.71) in <15 weeks of pregnant was significantly higher than that of 0.36 mg/L (95% CI: 0.25 to 0.48) in non-pregnancy ($P < 0.01$). The D-dimer levels ascended gradually with pregnancy ages, and reached a peak at 48–72 h post-partum with mean value of 6.44 mg/L (95% CI: 5.84 to 7.05), and then began to decline. The mean value of 0.78 mg/L at 1–8 weeks post-partum was approaching that of 0.36 mg/L (95% CI: 0.25 to 0.48) in non-pregnancy (Fig. 2A).

Normal fibrinogen reference values in pregnancy and post-partum

3284 normal pregnant women were included in 20 studies and reported fibrinogen concentrations in maternal blood in different gestational ages. Fibrinogen levels progressively increased during pregnancy, which was similar with D-dimer levels. The mean concentrations of fibrinogen was increased to 3.77 g/L (95% CI: 3.59 to 3.96) in pregnant <15 weeks, and reached a peak at 9.05 g/L (95% CI: 2.22 to 15.89) in 48–72 h post-partum, and then decreased to 3.62 g/L (95% CI: 3.03 to 4.20) at 1–8 weeks post-partum, which was approximately equal to 3.04 g/L (95% CI: 2.79 to 3.30) in non-pregnancy (Fig. 2B).

Normal F1+2 reference values in pregnancy and post-partum

The blood samples of 667 normal pregnant women in 6 studies were collected to determine the reference values of F1+2. F1+2 levels changed a little in the early pregnancy with mean value of 1.49 nmol/L (95% CI: 1.19 to 1.80), which was similar with 1.19 nmol/L (95% CI: 0.95 to 1.32) in non-pregnancy. F1+2 levels increased

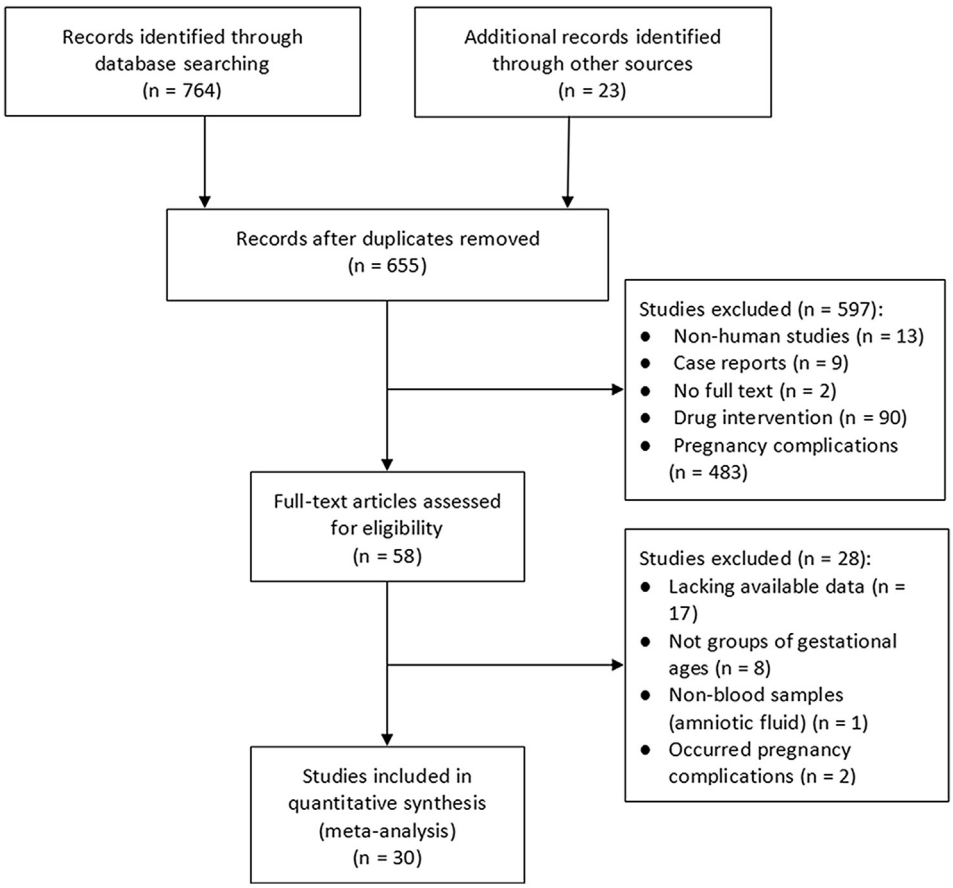

Fig. 1. Flow chart showing the study selection procedure.

from the middle of pregnancy, reached a peak in 29–36 weeks with mean value of 3.05 nmol/L (95% CI: 2.41 to 3.70) and then gradually decreased in the later pregnancy. It was close to the level of non-pregnancy in 1–8 weeks post-partum with mean value of 1.92 nmol/L (95% CI: 0.58 to 3.27) (Fig. 2C).

Discussion

We compiled available studies, reported haemostatic markers (D-dimer, fibrinogen and F1+2) in pregnancy and post-partum, and established convince gestational age related normal reference values. It also directly shows their dynamic trends during pregnancy and childbirth. According to the original gestational age, the heterogeneity in our study classified as <15 weeks, 12–28 weeks, 20–28 weeks, 29–36weeks, 36–42weeks, delivery, 24 h post-partum, 48–72 h postpartum, 1–8 weeks postpartum and non-pregnancy. D-dimer and fibrinogen levels gradually increased with the gestational age, peaked at postpartum 24 h and 48–72 h. F1+2 levels began to rise in the middle of pregnancy peak at 29–38weeks, and decrease at late pregnancy.

During pregnancy, compression ultrasound is the most widely used method of detecting DVT, which is sensitive to detect the lower extremity DVT. However, the iliac vein in the uterus is difficult to be detected by ultrasound. In addition, the blood vessels in inguinal and adductor muscles are difficult to be completely oppressed unless more force is applied, which may produce pain for patients. Impedance plethysmography (IPG) is used for the gravid uterus. The effect on venous return can produce false positive results. Magnetic resonance imaging (MRI) is superior to ultrasound in diagnosis of thrombus, but not as a routine test. Therefore, the establishment of normal value of pregnancy-associated coagulation markers is helpful to monitor the risk of thrombosis in pregnancy and to take appropriate preventive measures in time. Avoiding overtreatment and overdiagnosis also has an important clinical significance.

The threshold of D-dimer levels in normal non-pregnancy was considered as 0.5 mg/L [40,41]. However, it was not applicable to pregnant women. According to this study, D-dimer levels exceeded this threshold from early pregnancy to 1–8 weeks postpartum. Therefore, Kovac MK [6] and Kawaguch S [7] proposed D-dimer levels of 1.0 or 2.0 mg/L could be used as threshold in pregnancy. However, our results show that the D-dimer level decreased from 29–36 weeks to 36–42 weeks, even above 3 mg/L, which is consistent with Hedengran KK [8]. Nishii A [37] suggested that closely monitor, and prevention of VTE were needed, when D-dimer levels exceeded 3.2 mg/L during gestation. Based on it, our data shows that the most dangerous period of VTE was from partum to 48–72 h post-partum.

Morse M [27] came to conclusion that D-dimer levels started to increase markedly from the middle pregnancy, and there was no significant difference between early pregnancy and non-pregnancy. However, our results suggested that D-dimer levels notably rose from early pregnancy, and continued to elevate throughout the pregnancy, which was in line with Szecsi PB [29]. Xu D [9] concluded that there were no remarkable differences between D-dimer levels in early and later pregnancy. Choi JW [10] indicated that D-dimer levels in later pregnancy were five-fold higher than that in early pregnancy, which were consistent with this study. Our data illustrated that D-dimer levels peaked at 24 h post-partum and decreased at 48–72 h post-partum, which was consistent with the

Table 1
Characteristics of the eligible studies in the meta-analysis.

First author	Year	Country	Location or data source	Study design	Sample size	Mean age (year)	Group	Reported outcomes	Quality score
Comeglio P [14]	1996	Italy	University of Florence, outpatient clinic for prenatal care	Prospective non-randomized study	104	33 ± 4, 26 ± 3, 33 ± 5	3 trimesters of pregnancy and nonpregnant women	FBG, F1+2	7
Joly B [15]	2013	France	Grand Couronne and Mont Saint Aignan, Seine Maritime	Prospective non-randomized study	101	30 ± 5	3 trimesters of pregnancy	DD, FBG, F1+2, TAT, FMC	9
Onishi H [39]	2007	Japan	Kyorin University	Prospective non-randomized study	87	31.1–31.7	3 trimesters of pregnancy and nonpregnant women	DD, FMC, TAT	7
Cerneca F [16]	1997	Italy	Department of Gynaecology and Obstetrics of the University of Trieste	Longitudinal study	117	28.9 + 4.16	3 trimesters of pregnancy, Puerperium and nonpregnant women	FBG, F1+2, PT, aPTT, AT III, PC, PS, PAI, t-PA	7
Kovac MK [6]	2015	Serbia	Faculty of Medicine, University of Belgrade, Belgrade,	Prospective study	40	30 (22–40)	3 trimesters of pregnancy	DD, ETP, PS	6
Liu J [36]	2012	China	Outpatient and hospitalised women in Zhengzhou University Third Hospital,	Prospective non-randomized study	1130	20–44	Gestational age and nonpregnant women	FBG, PT, aPTT, TT	6
Bergmann F [21]	2014	Germany	Lab association Wagner stibbe, Amedes Group	Prospective non-randomized study	1022	N/A	Gestational age	DD	6
Wang M [40]	2013	China	Women's Hospital, School of Medicine, Zhejiang University	Prospective non-randomized study	1343	18–24	Gestational age and normal menstrual cycle women	DD	8
Liu XH [37]	2013	China	West China Second University Hospital	A prospective, sequential, longitudinal study	232	29.50 ± 3.30	3 trimesters of pregnancy and nonpregnant women	FBG, PT, INR, aPTT, aPTT ratio, FDP, PC	9
Reger B [25]	2013	Hungary	University of Pécs	Prospective non-randomized study	83	28.85 ± 4.3	Gestational age and nonpregnant women	DD, FBG	7
Gillman T [13]	1959	Africa	Antenatal clinic and lantenatal clinic and labour wards of King Edward VIII Hospital	Prospective non-randomized study	64	21–30	Gestational age, labour stage, postpartum and nonpregnant women	FBG, euglobulin-lysis-time	6
Haliloglu B [22]	2010	Turkey	Maltepe University Hospital and Dumlupinar University Hospital	Prospective non-randomized study	68	N/A	Gestational age and postpartum	DD, FBG, WBC, Hb, Platelet, HCY, Vitamin B12, PT, aPTT	8
Xu D [9]	2016	China	Women's Hospital, School of Medicine, Zhejiang University	Retrospective study	8367	28.9 ± 4.5	Gestational age and postpartum	DD	6
Kline JA [34]	2016	USA	Carolinas Medical Center	Prospective non-randomized study	50	31 (6)	Gestational age and postpartum	DD, FBG	7
Hedengran KK [8]	2016	Denmark	GentofteHospital	A longitudinal cohort study	801	31.9	Gestational age and postpartum	DD	8
Choi JW [10]	2002	Republic of Korea	Inha University Hospital	Prospective non-randomized study	436	21–39	Gestational age and postpartum	DD, AT III, tPA, TPS, PAI-1	7
Hui C [12]	2012	China	Sun Yat-sen Memorial Hospital of Sun Yat-sen University	Prospective longitudinal study	58	N/A	Gestational age and nonpregnant women	DD, FBG, F1+2, PT, APTT, TT, TXB2, TM, PAI-2, RI, PI, S/D	6
Kjellberg U [23]	1999	Sweden	Sahlgrenska University Hospital	Prospective longitudinal study	48	29 (23–40)	Gestational age and postpartum	DD, FBG, F1+2, APC,PS, PC, SF, Factor VIII, t-PA, PAI-1, PAI-2	6
Nishii A [38]	2009	Japan	Social Insurance Sagamino Hospital	Prospective non-randomized study	1131	N/A	First and third trimester	DD	6
Hansen AT [11]	2011	Denmark	Department of Gynaecology and Obstetrics at the Aarhus University Hospital	Prospective non-randomized study	55	≥18	Gestational age	DD, FBG, PS	8
Francalanci I [26]	1995	Italy.	Outpatient clinic for prenatal care of University of Florence	Prospective non-randomized study	108	16–24	Gestational age and nonpregnant women	DD, FBG	7
Sattar N [27]	1999	Uk	Obstetric care at Glasgow Royal Maternity Hospital	Prospective non-randomized study	12	29.5 ± 4.0	Gestational age	DD, lipid, oestradiol, t-PA, PAI-1, et al.	6
Clark P [17]	1998	UK	Glasgow Royal Maternity Hospital	Prospective non-randomized study	239	N/A	Gestational age	F1+2, PC, et al.	6
Morse M [28]	2004	UK	Alexandra Hospital,	Prospective non-randomized study	48	17–36	Gestational age and nonpregnant women	DD, FBG, APTT, PT	7
Hale SA [35]	2012	USA	University of Vermont	Prospective non-randomized study	34	18–40	Early and later pregnancy	DD, FBG,t-PA, PAI-1, et al.	6
Huissoud C [29]	2009	France	Croix Rousse University Hospital	Prospective observational study	104	29 (23–26)	Gestational age and nonpregnant women	FBG, PT, APTT, et al.	7

Szecsi PB [30]	2010	Denmark	Gentofte Hospital, University of Copenhagen,	A longitudinal cohort study	801	31.9	Gestational age and postpartum	DD, FBG, APTT, PT, PS, et al.	8
Bremme KA [31]	2003	Sweden	Karolinska Hospital	Prospective non-randomized study	26	–	Gestational age, postpartum and nonpregnant women	DD, FBG, PC, PT, PS, et al.	6
Murphy N [32]	2014	Ireland	Cork University Maternity Hospital	Cross-sectional study	760	31	Gestational age	DD	6
Uchikova EH [33]	2005	Bulgaria	Higher Medical Institue	Prospective non-randomized study	35	25.78 ± 5.63	Later pregnancy and nonpregnant women	DD, FBG, PT, APTT, et al.	6

Abbreviation: DD: D-dimer; FBG: fibrinogen; F1+2: prothrombin fragments 1+2; TAT: thrombin–antithrombin complexes; FMC: fibrin monomer complexes; PT: prothrombin time; TT: thrombin time; aPTT: activated partial thromboplastin time; AT III: antithrombin III activity; PC: protein C; PS: protein S activity; PAI-1: type 1 plasminogen activator inhibitor activity; t-PA: tissue-plasminogen activator antigen; ETP: endogenous thrombin potential; SF: soluble fibrin; FDP: fibrin/fibrinogen degradation product; INR: international normalized ratio; MPV: mean platelet volume; FN: fibronectin; TXB2: thromboxane B2; TM: thrombomodulin; RI: resistance index; PI: pulsatility index; S/D: systolic/diastolic ratio; N/A: not available.

Fig. 2. Combined normal reference values in pregnancy and post-partum. **A.** Gestational age-specified normal reference values of d-dimer concentrations (Mean, mg/L). **B.** Gestational age-specified normal reference values of fibrinogen concentrations (Mean, g/L). **C.** Gestational age-specified normal reference values of F1+2 concentrations (Mean, nmol/L). ***F1+2*** prothrombin fragments 1+2.

previous studies [8–10,29]. Fragments of trophoblast was gone into the pulmonary circulation by blood, and dissolved to release thromboplastin cause by disseminated intravascular coagulation during pregnancy. And then start the fibrinolytic system to clear blood clots and increase physiologic plasma D–D. It was of great significance to determining a threshold to exclude DVT in pregnancy. D-dimer level reached the highest value of 6.44 mg/l in 24 h postpartum, which was significantly higher than that of non-pregnant women. But below this value is relatively safe for pregnant women. Our data in different gestational age to establish a reference value can provide a certain basis.

Similar to D-dimer levels, fibrinogen levels rose gradually throughout the pregnancy, but peaked at 48–72 h post-partum and almost closed to normal at 1–8 weeks post-partum. Hansen AT [11] proposed fibrinogen levels started to rise from second trimester, while started to elevate from early pregnancy in our results, and significantly higher than non-pregnant women ($P < 0.01$), consistent with Hui C [12]. Our results and Gillman T [13] suggested fibrinogen levels were relatively stable at partum and 48 h post-partum. The fibrinogen levels were elevated in pregnancy. However, how to specify the reference range of values that do not need treatment is still a question. Our results provide a reference in clinical. Comeglio P [14] and Joly B [15] proposed F1+2 was sensitive haemostatic marker, started to rise from early pregnancy, obviously related to fibrinogen levels. However, Hui C [12], Cerneca F [16] and Clark P [17] considered that F1+2 levels started to rise at middle pregnancy. When to start recovery was also controversial. Hui C [12] indicated that it decreased in later pregnancy. Nevertheless, Cerneca F [16] suggested it obviously decreased at 48 h post-partum. In our study, F1+2 levels started to increase in the middle of pregnancy, peaked at 29–38 weeks, and descended in later pregnancy, which was consistent with Hui C. This fluctuation trend was out of sync with D-dimer and fibrinogen levels. Although F1+2 was not become a sensitive indicators during pregnancy. In our study, the establishment of reference value of F1+2 can provide early warning in clinical.

However, our research also has several limitations. Individual study might adopt different assays, instruments, nationalities and sample sizes, which might lead to heterogeneity. In order to reduce heterogeneity, we grouped according to specific weeks of the merger and obtained the relatively reliable results. Furthermore, our data originated from abstracted data that might be not sufficiently accuracy.

In conclusion, D-dimer and fibrinogen levels had a similar dynamic trend, increased progressively throughout pregnancy and peaked at 24 h and 48–72 h post-partum. F1+2 levels peaked at 29–38 weeks and decreased in later pregnancy. At present, there is still no universal haemostatic reference ranges during pregnancy and post-partum. So, further studies are needed in the future.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

Ethic approval

Not applicable.

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