A COMPARISON OF EARLY ONSET PRE-ECLAMPSIA AND LATE ONSET PRE-ECLAMPSIA

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Declaration

I, Moubiin Joomratee, hereby declare that this research is my work. I am submitting this research report for the degree Master of Medicine in Obstetrics and Gynaecology at the University of the Witwatersrand, Johannesburg. This research report has not been submitted before for any degree or examination at this or any other university.

This MMed research report is submitted in the format of a submissible research article. The article conforms to the author guidelines for the International Journal of Obstetrics and Gynaecology.

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Clinical articles- Cross sectional study

Title: A Comparison of Early onset Pre-eclampsia and Late Onset Pre-eclampsia.

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Synopsis: This study comparatively describes the pregnancy characteristics and outcomes of women who had early onset preeclampsia versus late onset preeclampsia

Key words: Early onset Preeclampsia, Late Onset Preeclampsia, Magnesium Sulphate, preterm birth, Apgar score, Mississipi classification, Tennnessee classification

Abstract

Background

Early onset pre-eclampsia (EOPE) occurs before 34 weeks while late onset pre-eclampsia (LOPE) occurs after 34 weeks. The maternal and neonatal outcomes has are different with EOPE having a higher frequency of maternal and neonatal complications.

Objectives

To compare the clinical presentations, laboratory parameters, maternal and neonatal outcomes in women with EOPE and LOPE.

Methods

This was a cross sectional prospective record review. Convenient sampling was performed every fifth day and recruited preeclamptic women that delivered at Chris Hani Baragwanath Academic Hospital (CHBAH) and Rahima Moosa Mother and Child Hospital (RMMCH). Descriptive statistics were employed.

Results

There were 104 women of which 64 (61.5%) had EOPE and 40(38.5%) had LOPE. A higher frequency of Posterior Reversible Encephalopathy Syndrome (P=0.040), blurred vision (P=0.009), headache (P=<0.001), eclampsia (P=0.011) and HELLP syndrome (0.004) was observed in EOPE. The number of still births (P<0.001), neonates with an APGAR of less than 7 at 5 minutes (p=0.001), and neonatal admissions (P=<0.001) were higher in EOPE. There was no difference in the outcome between the HIV positive and negative women

Conclusion

With EOPE, end organs appear to be more severely affected than in LOPE. The HIV prevalence between the two groups was comparable.

Abbreviations

AST	Aspartate Transaminase
CHBAH	Chris Hani Baragwanath Academic Hospital
DBP	Diastolic Blood Pressure
EOPE	Early Onset Pre-eclampsia
GA	Gestational Age
HELLP	Haemolysis Elevated Liver Enzymes Low Platelets
INR	International Normalized Ratio
IQR	Inter Quartile Range
IU	International Unit
IUGR	Intra Uterine Growth Restriction
ISSHP	International Society for the study of Hypertension in pregnancy
LOPE	Late Onset Pre-eclampsia
MgSO4	Magnesium Sulphate
MUAC	Mid Upper Arm Circumference
PE	Pre-eclampsia
PRES	Posterior Reversible Encephalopathy Syndrome
RMMCH	Rahima Moosa Mother and Child Hospital
SD	Standard Deviation
SBP	Systolic Blood Pressure

Introduction

Pre-eclampsia affects 2% to 8% of all pregnancies worldwide and hypertensive diseases occur in 13% of primigravid women (1). Globally, hypertension contributes to about 10% to 15% of maternal deaths (1).

Perinatal mortality is also high due pre-eclampsia and higher following eclampsia (1). In 2019, gestational hypertension was demonstrated in 7%, and pre-eclampsia/eclampsia in 6% of primigravid women in South Africa (2).

There are two subtypes of pre-eclampsia, namely Early onset pre-eclampsia (EOPE), which occurs before 34 weeks and late onset pre-eclampsia (LOPE) which occurs after 34 weeks (3). There is a paucity of information that compares maternal and fetal outcomes in EOPE versus LOPE. In particular, there is little literature about HIV seropositivity and the features of severity in EOPE and LOPE. Both maternal and fetal outcomes in EOPE have always been considered as generally worse (3-6). Zhu et al found that intra uterine growth restriction (IUGR) was present in 22.4% of women with severe pre-eclampsia and in 18.6% of women with chronic hypertension with superimposed pre-eclampsia(7). The study however did not mention what proportion of the affected women had EOPE and what proportion had LOPE.

While the short-term implications of EOPE and LOPE usually affect the maternal and neonatal outcomes, observational studies have shown that in the long term there is usually an increased lifetime risk of cardiovascular disease in women who experience raised blood pressure in pregnancy (6). Wu et al found that pre-eclampsia is associated with a four-fold increase in the likelihood of cardiac failure later on and a two-fold increase in the likelihood of developing coronary heart disease, stroke and death (8).

It has been suggested that EOPE is usually due to impaired trophoblastic invasion, whilst LOPE is usually associated with hypoperfusion of the placenta(9). The severity of pre-eclampsia is directly proportional to the extent of abnormal trophoblastic invasion, which leads to placental hypoperfusion and the release of systemic vasoactive compounds. These compounds contribute to an inflammatory reaction, vasoconstriction, endothelial damage, capillary leakage, hypercoagulability and platelet dysfunction(10).

A screening approach involving the assessment of multiple factors linked to pre-eclampsia was suggested by Poon LC et al, with two broad categories including either early screening at 11 to 13 weeks or late screening at 30 to 33 weeks' gestation (11). They postulated that the incidence of pre-eclampsia and the gestational age at which it occurred was strongly dependent on the risk factors associated with the index pregnancy (11). As per their hypothesis, a woman described as having little or no risk of developing pre-eclampsia would in theory, still develop pre-eclampsia at around 54 weeks should her pregnancy be allowed to continue indefinitely. In the group of women described as having a high probability of developing pre-eclampsia, the chances of developing pre-eclampsia prior to 34, 37 and 42 weeks were 36%, 33% and 29% respectively(11).

This study was thus conducted to compare the clinical manifestations, laboratory biomarkers, maternal and neonatal outcomes in women with EOPE and LOPE.

Material and methods

This was a cross sectional study done with data with prospectively collected from women with pre-eclampsia who delivered at Chris Hani Baragwanath Academic Hospital (CHBAH) and Rahima Moosa Mother and Child Hospital (RMMCH). The sampling method was one of convenience. The data was collected by the researcher on his post-intake days and was entered in an Excel spreadsheet CHBAH is a tertiary hospital and RMMCH a specialised regional hospital; both are academic hospitals affiliated to the University of the Witwatersrand. In 2019 there were 19182 deliveries at CHBAH(12), while RMMCH had 14 199 deliveries(13). Data was collected from 1st of December 2020 to 30th of April 2021 post-delivery in the high care ward as well as in the postnatal wards of these hospitals. Women were counselled and recruited only after consent was obtained (Refer to appendix B for participant consent sheet). This was a convenient sample conducted on the day the researcher was on call. Data was extracted from the medical records and captured in a REDCAP data base.

The 2019 National Guideline for hypertension in pregnancy was used to classify the various forms of hypertension. Chronic hypertension was defined as Hypertension predating pregnancy or diagnosed before a gestational age of 20 weeks (14). Gestational hypertension was defined as new onset of hypertension after 20 weeks of gestation (14). Pre-eclampsia was defined as blood pressure equal to, or more than 140/90 mmHg accompanied by one of the following: proteinuria or evidence of organ dysfunction after the 20 weeks of gestation or IUGR (14).

Proteinuria was considered significant and present if ≥0.3g over 24 hours, or urine protein to creatinine ratio of ≥30mg/mmol, or urine dipstick protein of ≥1+. Renal dysfunction was defined by a creatinine of ≥ 100μmol/L, or a serum urea of >8 mmol/L (14). Two sets of criteria were used to assess the impact on the liver and platelet count; first the Tennessee classification where an AST of at least 70 (U/L) and a platelet count of less than 100 (10^9/L) is considered abnormal. As per the Tennessee classification, true or complete HELLP syndrome was defined by platelet < 100,000, AST>70IU/L, LDH>600IU/L. Partial or incomplete HELLP included severe preeclampsia with any one of the following: ELLP, HEL, EL, LP) (15). At the University of the Witwatersrand institutions, a platelet count of< 150, an AST/ALT of >40IU in the presence of haemolysis is used to identify women with HELLP syndrome (16). Haemolysis was confirmed by the clinician at the time of diagnosis by either one of the following: presence of coke coloured urine, increase LDH, reduced haptoglobin or an increase in the unconjugated bilirubin.

Intra uterine growth restriction was diagnosed at birth if the baby had a birth weight below the 10th percentile for gestational age. The world health organisation growth chart was used. The birth weight and gestational age at birth were compared and the birth weight assigned to the relevant centile depending on the gestational age at birth. The measure of neonatal outcomes were birth weight, APGAR score, live or stillbirth.

The study was performed after approval from the Human Research Ethics Committee of Wits University, HREC Number M200806 and permission granted by the CEOs of both hospitals where the research was done. The NHRD number was GP202007042.

All analyses were completed using SPSS Version 27. Means and standard deviations were used to describe continuous variables, whilst categorical variables were described using frequencies and percentages

Independent sample *t*-tests were used to assess differences in continuous outcome variables. Chi-square tests were used to determine differences between categorical outcome variables. The level of significance for all analyses was set at $p = <0.05$.

The objectives of this study were to: describe and compare the various clinical presentations and outcomes, laboratory outcomes, obstetrical and physical parameters in women with EOPE and LOPE; and to describe and compare the fetal and short term neonatal outcomes in early and late pre-eclampsia

Results

A total of 104 women were sampled and consented for the study. Women were stratified into early and late onset preeclampsia Of the 104 women who were assessed, 64 had EOPE and 40 had LOPE. Table 1 outlines the demographic characteristics of women in the study. All the women were of black ethnicity. There was 18.8% of the women in EOPE and 18.0% of the women in LOPE who were HIV seropositive, p= 0.872.

Table 1: Demographic Data

Variable	EOPE Mean ±SD Median (IQR) Number (%) n=64	LOPE Mean ±SD Median (IQR) Number (%) n=40	P value
Age in years	29.69 ±7.30	29.35 ±6.51	0.811 *
Booking haemoglobin(g/dl)	12.04 ±1.83	11.55 ±2.31	0.244 *
GA at booking in weeks	18.57 ±7.68	19.48 ±8,86	0.564 *
DBP at diagnosis in mmHg	108.86 ±16.4	96.73 ±15.1	**<0.001** *
BMI at diagnosis in kg/m^2	30.04 ±5.81	30.46 ±7.40	0.380
Parity	1(0-2)	1(1-2)	0.330 *
Gravidity	2(1-4)	2(2-3)	0.688 *
Weight in kilograms	76.0(66.0-85.3)	72.4(85.4-87.7)	0.751 *
SBP at booking in mmHg	133.5(122.7-148.5)	132(114.5-139.2)	0.107 *
SBP at diagnosis in mmHg	170.0(155.0-185.3)	154.5(145.8-167.3)	**<0.001** *
DBP at booking mmHg	81(72.0-95.7)	79.5(70.7-86.2)	0.226 *
HIV seropositive	12 (18.8%)	7 (18.0%)	0.919 †
Rhesus positive	60 (93.8%)	40 (100%)	0.107 †

GA=gestational age, DBP=diastolic blood pressure, BMI= body mass index, SBP=systolic blood pressure,*Independent Sample t-test,† Chi-Square test

In Table 2, of the 60 EOPE women that had measured creatinine prior to delivery, 10 (17%) had a creatinine of > 100 μmol/L, whilst one (2.5%) of the 39 LOPE women had a creatinine > 100 μmol/L, p = 0.046. There was no statistically significant difference in the comparison of urea in EOPE versus LOPE, with a p= 0.142.

The Tennesse classification which has a platelet threshold of 100, identified 15 fewer HELLP syndrome in the EOPE and 6 fewer in the LOPE group than the WITS ptotocol. The use of an AST threshold of 40 IU, also used by Wits medical institutions, identified 8 more women with deranged liver enzymes in EOPE and 6 more women with deranged liver enzymes in LOPE. 37 patients were diagnosed with HELLP syndrome using the Wits criteria and 30 patients were diagnosed with HELLP syndrome using the Tennessee criteria.

Table 2 Haematology and biochemistry results prior to delivery

Laboratory parameter Prior to delivery		EOPE		LOPE		P value
		n	No (%)	n	No (%)	
AST in IU	> 70	57	18 (31.6)	36	2 (5.5)	0.004 †
	> 40	57	26 (45.6)	36	8(22.2)	0.023 *
ALT in IU	> 40	58	24 (41.4)	37	1 (2.7)	<0.001
Platelet count x10^3 cells/mm^3	<150	60	27 (45.0)	39	10 (25.6)	0.051 *
	<100	60	12 (20.0)	39	4 (10.3)	0.268 †
	<50	60	6 (10.0)	39	1 (2.6)	0.240 †
Creatinine (μmol/L)	>100	60	10 (16.7)	39	1 (2.6)	0.046 †
Urea (mmol/L)	> 8	60	7 (11.7)	39	1 (2.6)	0.142 †

AST= aspartate aminotransferase, ALT= alanine transaminase,* Chi-square tests; † Fishers exact tests

Eclampsia, Posterior Reversible Encephalic Syndrome, blurred vision and headache were observed more frequently in women with EOPE (Table 3). There was no statistically significant difference in the frequency of abruptio placenta or proteinuria in EOPE versus LOPE. The development of HELLP syndrome and the use of magnesium sulphate in EOPE was more frequent than in LOPE. The caesarean section rate was significantly higher among women with EOPE than LOPE with an a rate of 84.8% versus 67.5% respectively, p-value= 0.028. The indication for caesarean section was however not taken into consideration when the template for data collection was designed. No maternal death was identified in either group.

Table 3: Clinical manifestations and interventions in EOPE and LOPE

Variables	EOPE		LOPE		P value
	n	No(%)	N	No(%)	
Eclampsia	62	9 (14.5)	40	0 (0.0)	**0.011** †
PRES	62	7 (11.5)	40	0 (0.0)	**0.040** †
Blurry vision	62	30 (48.4)	40	9 (22.5)	**0.009** *
Headache	64	45 (70.3)	40	15 (37.5)	**<0.001** *
Abruptio placenta	64	7 (10.9)	40	1 (2.5)	0.149 †
Proteinuria	63	48 (76.1)	40	25 (62.5)	0.145 *
Use of magnesium sulphate	64	51 (79.7)	40	22 (55.0)	**0.007** *
Caesarean section	64	54 (84.8)	40	27 (67.5)	**0.028** *
HELLP syndrome	64	25 (39.0)	40	5 (14.3%)	**0.004 †**

PRES= Posterior Reversible Encephalic Syndrome, HELLP= Haemolysis Elevated Liver enzymes Low Platelets, *Chi Square Test; †Fisher's exact test

Neonatal outcome

The adverse neonatal outcomes were more frequent in EOPE than LOPE (Table 4). The number of birth weight below the 10th centile and the frequency of low Apgar scores at 5 minutes were higher for EOPE than LOPE. There was however no statistically significant difference between the number of foetuses with low birth weight in EOPE versus LOPE. The average gestational age at delivery of EOPE was 30.6 weeks and the average gestational age at delivery of LOPE was 37.3 weeks. The early gestational age of delivery in EOPE could be a contributing factor for the lower Apgar scores.

Table 4: Neonatal outcome

Neonatal Outcomes		**EOPE n=64**		**LOPE n=40**		**P value**
		n	No (%)	N	No (%)	
NICU admission		63	38 (60.3)	40	6 (15.4)	**<0.001***
Birth weight < 10th percentile		58	30 (51.7)	39	19 (48.7)	0.772*
APGAR < 7 at 5 minutes		62	20 (32.3)	39	2 (5.1)	**0.001†**
Outcome	Alive	64	44 (68.7)	40	39 (97.5)	**<0.001†**
	Stillbirth	64	20 (31.3)	40	1 (2.5)	

NICU= Neonatal Intensive Care Unit, *Chi-Square Test, †Fisher's exact test

Discussion

There were a total of 104 women with pre-eclampsia, of which 64 had EOPE and 40 had LOPE with a ratio of EOPE to LOPE of 1.6:1. A disparity in proportions of EOPE and LOPE has been reported in other countries. In 2013, a study from Washington State in the United States of America reported a ratio of EOPE to LOPE of 1: 7.1 (17). A cohort from 2001 to 2014, in Taiwan reported a ratio of EOPE to LOPE of 1:1.4 (18). The difference between the values of the ratio of EOPE to LOPE from these studies and ours could be due to the difference in the ethnic distribution of these countries and South Africa. All women included in our trial were of black ethnicity, which is known to predispose these women to a higher risk of developing pre-eclampsia (19).

The two main objectives were to describe and compare the clinical presentations, and laboratory parameters in women with EOPE and LOPE as well as to describe and compare the neonatal outcomes in EOPE and LOPE. These were compared with five other studies. The Tennessee criteria was used to assess HELLP syndrome and WITS criteria for HELLP syndrome was used as a comparison

It was found that deranged biochemical and haematological findings, as assessed by the Tennessee classification, were more frequently observed in EOPE than LOPE. The AST was raised in 45.6% EOPE vs 22.2% of LOPE , p=0.023. The ALT was raised in 41.4% of EOPE vs 2.7% of LOPE, p<0.001 and creatinine levels were higher than 100 μmol/L in 16.7% of EOPE vs 2.6% of LOPE, p=0.046. W´ojtowicz A et al, in a Polish study, found no statistically significant difference between the AST and ALT levels of EOPE versus LOPE, although they found a higher prevalence of women with creatinine higher than 90μmol/L in EOPE as opposed to LOPE, p=0.001(3). Li XL et

al, in a Chinese study, found a similar conclusion to the Polish study (3)(20). They found no statistically significant difference when investigating liver enzymes but found that the median creatinine level in EOPE was higher than the median creatinine level in LOPE, p=0.003 (20).

With regards to the central nervous system, a higher proportion of women with EOPE developed blurry vision (48.4% versus 22.5%, p=0.009), PRES (11.5% vs 0.0%, p=0.040) and eclampsia (14.5% vs 0.0%, p=0.011) respectively. W´ojtowicz A et al however found a different conclusion when they compared the occurrence of eclampsia in EOPE versus LOPE, with p-value described as being non-significant in their studies (3).

In the current study, EOPE also had a higher frequency of adverse neonatal outcomes as compared to LOPE. There was a higher proportion of stillbirth in EOPE versus LOPE (31.3% versus 2.5%, p<0.001) and a higher proportion of APGAR <7 at 5 minutes in EOPE versus LOPE (32.3% versus 5.1%, p=0.001). W´ojtowicz A et al also pointed to a higher prevalence of low APGAR in EOPE versus LOPE (p<0.001) as well as a higher proportion of stillbirth in EOPE versus LOPE (p<0.001) (3). Li XL et al also found that the prevalence of stillbirth was statistically higher in EOPE versus LOPE, p=0.001. (20) While the index study did not find any difference in the prevalence of IUGR in EOPE and LOPE, the Polish study did find such an association with a higher occurrence of IUGR in EOPE with p=0.0015 (3). A similar finding was found in a Taiwanese study by Tai-Ho Hung which showed a higher prevalence of IUGR in EOPE than LOPE, p<0.001 (4).

There were two main interventions, namely the use of MgSO4 and Caesarean section. The use of MgSO4 was more frequent in EOPE than in LOPE (79.7% versus 55.0%, p=0.007) and there were more caesarean sections done in women with EOPE than women with LOPE (84.8% versus 67.5%, p=0.028). Patients with EOPE delivered on

average earlier (average GA of 30.6) than patients with LOPE (average GA of 37.3) which could explain the higher incidence of adverse neonatal outcomes in neonates born to mothes with EOPE. Women with EOPE are inherently at risk of caesarean section and magnesium sulphate used and this is associated with the disease severity rather than the use of MgSO4 or caesarean section.

Amongst the parameters assessed on presentation we found that only the systolic blood pressures at diagnosis were significantly higher in EOPE (median of 170.0mmHg) as opposed to LOPE (median of 154.5mmHg), $p<0.001$ EOPE appears to be associated with a higher frequency of adverse clinical signs and laboratory parameters.

It has been suggested that the pathophysiology of EOPE is different to LOPE. EOPE is more associated with placental factors (3).This contrasts with Poon LC et al who suggested that the time of onset of pre-eclampsia was related to the risk of the women developing the pathology. Their study suggested that women at higher risk would develop pre-eclampsia earlier; hence having a higher risk of developing EOPE (11).

There were limitations in this study. The first limitation is that it is a cross-sectional study. Secondly, it was a convenient sampling with a realtively small sample size. However, the strength of our study was that the entire sample was from a black population which differed from other studies done in the northern hemisphere where the population is predominantly Caucasian. We also have a higher prevalence on HIV seropositive women in South Africa which allowed us to explore differences in the prevalence of HIV seropositivity in EOPE versus LOPE although no statistically significant difference was found between the prevalence of HIV in either EOPE or LOPE. The third limitation was the fact that a convenience sampling was taken.

Conclusion

With EOPE, end organs appear to be more severely affected than in LOPE. The proportion of morbidity and mortality was higher in EOPE than in LOPE. The clinical signs and symptoms upon presentation, the biochemical and haematological parameters were all worse in early onset preeclampsia in comparison to late onset preeclampsia. Eclampsia and abruptio were also more prevalent among EOPE than LOPE although the association was statistically significant only with Eclampsia. EOPE was also associated with adverse fetoplacental conditions since there was a strong association between low Apgar at 5 minutes and stillbirth.

Women with EOPE need careful management ideally as they are at high risk of poor outcomes. We also need to train all levels of healthcare workers who provide antenatal care about the risks associated with EOPE, especially its higher risk of morbidity and mortality. Bigger similar studies need to be conducted in South Africa to confirm our findings. Systemic reviews and meta analyses could also be carried out to confirm our study findings.

Author contributions

M Joomratee wrote the 1st draft. All the other others made contribution to the revision of the manuscript. All authors made the criterias to be included as authors.

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Protocol

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ISSHP	International Society for the study of Hypertension in pregnancy
LOPE	Late Onset Per-eclampsia
PE	Pre-eclampsia
PRES	Posterior Reversible Encephalic Syndrome
RMMCH	Rahima Moosa Mother and Child Hospital
SD	Standard Deviation

Background

Pre-eclampsia affects 7% of pregnancies worldwide (1). Hypertensive diseases in pregnancy occurred in 12.5% of primigravid women. Gestational hypertension affected 6.7%, pre-eclampsia and eclampsia affected 5.75% of primigravid women (2). In an article published in 2018, it was found that in the province of Kwazulu - Natal, in South Africa, the incidence of patients diagnosed with pre-eclampsia was about 12.3%. Of these,19.9% were early onset and 80.1% were late onset (3). Pre-eclampsia is currently one of the leading factors of maternal and perinatal death and complications in both developed and developing nations (4). Globally it represents about 20% of maternal deaths and is associated with about 15% of preterm deliveries (4). In South Africa, the Saving Mothers Report (2017) indicated that hypertension in pregnant women is associated with 14.8% of all maternal deaths. The most frequent causes of death were cerebral haemorrhage and pulmonary oedema (5), while an article that appeared in the South African Medical Journal in August of 2016 held cerebral injury as the cause of death in more than 50% of hypertensive maternal mortality cases (6).

Its effect on the fetus is also quite significant. The utero-placental insufficiency contributes to undernutrition of the fetus which causes growth retardation. There are both short- and long-term effects associated with growth retardation. The short-term effects on the fetus include: intrauterine growth restriction, premature delivery and an increased probability of stillbirth or miscarriage (7). As for the long-term

consequences, it can, later in adult life, lead to cardiovascular diseases which include hypertension, cardiovascular disease and diabetes (7).

The exact pathophysiology responsible for preeclampsia is unclear. One of the postulated theories is that abnormal placentation can lead to the development of preeclampsia. Placental implantation with abnormal trophoblastic invasion of uterine vessels is one the major causes of preeclampsia. The extent of abnormal trophoblastic invasion is directly related to the severity of the disease. This leads to placental hypoperfusion and the release of systemic vasoactive compounds. These compounds leads to an inflammatory reaction, vasoconstriction, endothelial damage, capillary leakage, hypercoagulability and platelet dysfunction (8). Early onset pre-eclampsia is usually due to impaired trophoblastic invasion and late onset pre-eclampsia is usually due to hypoperfusion of the placenta (9).

Early and Late onset pre-eclampsia

Early pre-eclampsia occurs before 34 weeks while late onset pre-eclampsia occurs after 34 weeks (10).

A Polish study concluded that early onset pre-eclampsia was strongly linked to fetal growth restriction and vascular flow disturbances. Impaired placentation was suggested to be a likely contributing factor. The study also found that the incidence of neurological, cardio-respiratory and haematological complications in women with EOPE was different to that of woman with LOPE (11). In a cohort from Utrecht, women with previous EOPE compared with women with LOPE and pregnancy-induced hypertension had significantly higher fasting blood glucose, higher insulin, and higher cholesterol levels. More women with EOPE later developed chronic hypertension than women with LOPE (12).

There are many studies that have been done in other institutions worldwide that compare EOPE against LOPE.

These are summarized below.

Table: Summary of the studies comparing early vs late-onset pre-eclampsia

Study	Major findings
Early and Late Pre-eclampsia: A Comprehensive cohort study of Laboratory and Clinical findings according to the new ISSHP criteria (11). N=214	• Early onset preeclampsia was linked to negative fetoplacental outcomes, which included intra uterine growth restriction and intrauterine fetal distress. • EOPE was associated with an APGAR of less than 7 at 1 minute and 5 minutes. • EOPE was linked to higher creatinine level and higher proteinuria over 24 hours as opposed to LOPE.
Incidence of Pre-eclampsia: risk factors and outcomes associated with early versus late-onset disease (15). N= 456,668	• In EOPE, fetuses were small for gestational age. • LOPE was linked with diabetes mellitus

Cardiovascular disease risk factors after early-onset pre-eclampsia, late onset pre-eclampsia and pregnancy induced hypertension (12). N= 524	• Patients with EOPE had an increased lifetime risk of lipodystrophy, insulin resistance and chronic hypertension • Patients with EOPE had Small for Gestational age fetuses, and younger maternal age.
Risk of abnormal Fetal growth in women with early and late onset pre-eclampsia (13). N= 29494	• Strong association between EOPE and babies born small for gestational age. • Association between late onset pre-eclampsia and fetuses born large for gestational age, possibly due to some confounding factors
An analysis of the differences between early and late pre-eclampsia (14). N= 177	• No significant association between Fetal growth restriction and either form of pre-eclampsia. • However, there was a strong association between EOPE and stillbirth and higher creatinine level

Pathogenesis of pre-eclampsia and factors predisposing to pre-eclampsia

As mentioned above, one of the postulated theories is that abnormal placentation can cause pre-eclampsia (7). Furthermore, there is also an imbalance between utero-placental supply and fetal demands, which results in both maternal and fetal affectations. The maternal affectations include several organ systems which are the cardiorespiratory system (chest pain, dyspnoea, decrease in oxygen saturation, myocardial infarction and infarction), central nervous system (headache, eclampsia, PRES), renal (acute kidney injury, raised uric acid and creatinine), hepatic (nausea and vomiting, epigastric pain, raised liver enzymes, raised INR, hepatic rupture) and the haematological system (thrombocytopaenia) (16). Women with pre-eclampsia have raised Thromboxane A2 as opposed to prostacyclin which leads to vasoconstriction and platelet aggregation (17).

Fetal affectations include oligohydramnios, intra uterine growth restriction, abnormal umbilical artery Doppler velocimetry, lower fetal middle cerebral artery resistance, abnormal ductus venous waveform and stillbirth (16). There are many factors that predispose to PE. These are advanced age, hypertension, high blood lipids, diabetes mellitus, raised body mass index, parity and gravidity, a history of pre-eclampsia and lack of prenatal care (18,19).

Screening and prevention of pre-eclampsia

A multivariate screening approach was suggested by Poon et al for pre-eclampsia (20). They divided it into two broad categories which include early screening at 11 to 13 weeks and late screening at 30 to 33 weeks (20). They assume hypothetically, that should any pregnancy be able to continue forever, then any woman would develop pre-eclampsia (20). However, the rate of onset of pre-eclampsia is strongly dependent on the risk factors associated with the index pregnancy. In their hypothetical model, a woman described as having a low risk of developing

preeclampsia would in theory still develop pre-eclampsia at around 54 weeks should her pregnancy be allowed to continue indefinitely. On the other hand, they also found, in the group of women described as having a high probability of developing PE, the chances of developing preeclampsia prior to 34, 37 and 42 weeks were 36%, 33% and 29% respectively (20).

One of the parameters explored was the mean arterial pressure itself. They are of the opinion that the higher blood pressure in patients predisposed to pre-eclampsia can be observed as early as the first trimester itself, meaning that screening for some parameters in the first trimester itself can be useful. They concluded that predicting the occurrence of pre-eclampsia through screening as early as the 1st trimester can have a success rate as high as 95% for a false positive of ten percent. (20).

The American College of Obstetrics and Gynaecologists however do not advise on screening to predict pre-eclampsia beyond obtaining any relevant and medical history. The college further advise that any additional benefit of screening, including biophysical tests, biochemical markers, must be able to justify the extra costs. The college also suggest that any first trimester evaluation of preeclampsia will only be of any benefit if they have sensitivities and positive predictive values which are high enough to clinically benefit the woman and to offset the cost associated with performing the test (21).

With regards to the use of aspirin in women at higher risk of developing PE, a study done at the University of Colorado School of Medicine concluded that low dose Aspirin initiated at less than 17 weeks decreased the risk of late onset pre-eclampsia ($p=0.047$) (22).

Problem Statement & justification of the study:

Pre-eclampsia and eclampsia were found to affect about 5.75% of all primigravida's in South Africa (2). Hypertensive disease in pregnancy was thought to cause 14.8% of the maternal deaths in South Africa (5). The maternal, fetal and perinatal effects as well as the long-term outcomes in EOPE versus LOPE have been shown to be different. (11,12,13,14,15). It is important to see whether these differences exist in a South African population.

Aim

The aim of the study is to compare the pregnancies and their outcomes of women with EOPE versus LOPE over a two month period.

Specific Objectives

- To describe and compare the various clinical presentations and outcomes, laboratory outcomes, obstetrical and physical parametres in patients with EOPE and LOPE
- To describe and compare the fetal and short term neonatal outcomes in early and late pre-eclampsia

Methodology

This will be a prospective study.

We will identify patients who have been admitted for pre-eclampsia or eclampsia and who are post-delivery in the post-natal wards. The aim is to gather a total of 200 files over a span of 4 to 6 months. The number of files collected in each hospital will be proportional to the number of births in each hospital per year.

Study Setting

Chris Hani Baragwanath Academic Hospital (CHBAH) is a tertiary academic hospital that provides Obstetric and Gynaecological services and receives referrals from several regional and district hospitals within the province of Gauteng. The latest annual statistics for CHBAH indicates annual delivery of 17,000 babies, 4160 caesarean sections, 700 still births and 3500 low birth weight babies (23). Rahima Moosa Mother and Child Hospital (RMMCH) is also a regional academic hospital that provides Obstetric and Gynaecological services within the province of Gauteng. In 2019, there were 14199 deliveries at RMMCH which included 5093 caesarean sections, 210 still births, a perinatal mortality rate of 25.8 per 1000 and 2078 low birth weight babies (less than 2.5kg) (24).

Study Population

The Study population will include pregnant women with pre-eclampsia that are admitted. Early onset pre-eclampsia will be defined as women who developed preeclampsia before 34 weeks and Late onset pre-eclampsia as those who developed at or after 34 weeks.

Data Management

The data that will be collected as shown in table 2

Table 2: Data that will be collected

Obstetric factors	Age, Parity,gravidity, booking bloods, History of poor obstetric history, Gestational Age (GA) at booking, GA at diagnosis of PE, GA at delivery
Co-morbidities	Epilepsy, Asthma, diabetes, Gestational Diabetes, Poor Obstetric History, Anti-Phospholipid Syndrome, Chronic Hypertension
Delivery	Mode of delivery and if Caesarean section; reason for caesarean section
Maternal factors	Proteinuria, HELLP Syndrome, Neurological affectations, Renal affectation, Liver involvement
Fetal factors	Intra Uterine Growth Restriction
Neonate	Live birth or Still Birth, APGAR at 5 minutes.

Definitions:

The 2019 National Guide line for hypertension in pregnancy will be used to classify the various forms of hypertension. These are as follows:

- Chronic Hypertension: Hypertension predating pregnancy or diagnosed before a gestational age of 20 weeks (25).
- Gestational Hypertension: New onset of hypertension after 20 weeks of gestation (25).

- Pre-eclampsia: Blood Pressure of equal or more than 140/90 mmHg accompanied by proteinuria or evidence of organ dysfunction after the 20 weeks of gestation (25).

NOTE: The guideline highlighted the fact that proteinuria is not mandatory to diagnose of PE (25). In our study, the preeclamptic patients may or may not have proteinuria.

Renal disease will be defined as a minimal proteinuria of 0.3g over 24 hours or a minimum urine protein to creatinine ratio of 30mg/mmol or a urine dipstick protein of >1+, and renal dysfunction with a creatinine of at least 120μmol/L (16).

The Tennessee classification will be used to assess for Liver involvement as well as thrombocytopenia. The HELLP criteria will be an AST of at least 70 (U/L) and a platelet count of less than 100 (10^9/L). (26)

Intra Uterine Growth Restriction will be diagnosed at birth if the baby has a birth weight which falls below the 10^{th} centile (27).

Data Analysis

All categorical variables will be described using frequencies and percentages. Comparisons of these will be performed using chi2. Continuous variables will be described using means (with SD) and medians (with IQR). These will be compared using the Student t test or the Wilcoxon Rank test.

Ethics

The protocol will be submitted to the Human Research Ethics Committee of Wits University and the CEO's of Chris Hani Baragwanath Academic Hospital and

Rahima Moosa Mother and Child Hospital for approval. Patients will be informed about the study prior to accessing their file. Patients who have had a poor outcomes are as a routine offered counselling, this offer will be repeated if during the consent process they are emotionally distressed. A separate sheet with the study number and patient details will be kept.

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Appendix A

DATA CAPTURE SHEET			
Study number			
Date of enrolment			
Consent obtained			
Early or Late Onset Pre-eclampsia	Early	Late	
Age			
Parity			
Gravidity			
HIV status	Positive	Negative	Unknown
ART	Yes	No	
Rhesus	Positive	Negative	Unknown
Booking Weight		Not done	
Height		Not done	
MUAC		Not done	
Booked	Yes	No	
Haemoglobin at booking		Not done	
LMNP	Date:		
Certain of date of LNMP	Yes	No	
First Ultrasound	Date:		
	GA	EDD	
If no LNMP and no US, GA by palpation		Not done	
Gestational Age at booking (calculate with ACOG)			
Gestational Age at diagnosis (calculate with ACOG)			
Blood pressure	At Booking	At Diagnosis	
Systolic Blood pressure			
Diastolic Blood pressure			

Maternal and Fetal Affectations	Yes	No	Not done/unknown
Eclampsia			
Posterior Reversible Encephalopathic Syndrome			
Maternal and Fetal Affectations	Yes	No	Not done/unknown

Blurry vision			
Headache			
Pulmonary Oedema			
Any focal neurological sign			
Abruption			
Proteinuria			
Use of Magnesium Sulphate			
Celestone			
Neonatal Admission			
Live or Still Birth			
Apgar at 5 minutes			
Gestational age at delivery			
Birth Weight			
Mode of delivery			
Reason for caesarean section			

Comorbidities	Yes		No	
Asthma				
Epilepsy				
Diabetes				
Poor Obstetrics History *				
Anti-Phospholipid Syndrome				
Chronic Hypertension				
Diabetes	Type1	Type2	Gestational	nil
Aspirin during pregnancy	Yes		No	
	GA started			

Biochemistry	Last recorded prior to delivery	First recorded after delivery
Urea		
Creatinine		
AST		
ALT		
Platelet		
Haemoglobin		

∗Poor Obstetric History will be defined as two or more first trimester miscarriages, one or more 2nd trimester miscarriages, Intra Uterine Death, Fetal loss, neonatal loss

Abbreviations

ALT	Alanine Transaminase
ART	Anti Retroviral Therapy
AST	Aspartate Transaminase
EDD	Estimated Date of Delivery
GA	Gestational Age
LNMP	Last Normal Menstrual Period
MUAC	Mid-Upper Arm Circumference
US	Ultra Sound

Appendix B

PARTICIPANT CONSENT SHEET

Title of Study: A Comparison of Early Onset Preeclampsia and Late Onset Preeclampsia

1. I have been given information which explains the nature and processes involved in this study, which is written below;
2. I was given time to read it, or had it read to me, in the language I best understand;
3. I was given time to ask any questions I wanted to and found any answers given to me to be reasonable and satisfactory;
4. I believe I fully understand why the study is being conducted and what the intended outcomes will be;
5. I understand that there will be no immediate benefit to me, should I agree to participate, nor will I receive any payment; conversely, participation will not cost me anything but my time;
6. I understand that, even if I initially consent to take part in the study, I may subsequently withdraw at any time and would not be required to give any reasons; if that happened, any data collected about me for the purposes of the study would immediately be destroyed, unless I give consent for it to be retained
7. I have been given a range of contact details, listed below. If I require further information or become concerned about any aspect of this study I am free to speak to any of these contacts.

Information for Patient:

A significant proportion of pregnant women are affected by hypertension in South Africa. As a patient affected by hypertension in pregnancy, we would like your participation in this study. We would like to know how hypertension has affected you and your baby during your pregnancy. We request permission to examine your file to access the relevant information for the study. I will not be involved in your management or your baby's management in the ward. The study aims to compare the various maternal parameters, fetal and immediate neonatal outcomes associated with early and late onset preeclampsia. The aim of the study is to better understand

and eventually better manage the pathology of preeclampsia, thereby decreasing the morbidity and mortality associated with such a pathology in future pregnancies.

Contact details:

Dr Joomratee, Principal Investigator, telephone no. 0649071744,

Prof Adam, Supervisor, telephone no 0832602638

Dr Wise, Co Supervisor, telephone no 0731527513

Dr Naidoo, Co Supervisor, telephone no 0829269077

Professor CB Penny, Chairperson of the Human Research Ethics Committee (Medical) at the University of Witwatersrand, on telephone no. 011 717 2301, or by e-mail at Clement.Penny@wits.ac.za.
Ms. Z Ndlovu or Mr Rhulani Mkansi, Committee Secretariat, telephone nos.: 011 717 2700 or 1234, or by e-mail at: Zanele.Ndlovu@wits.ac.za or Rhulani.Mkansi@wits.ac.za

Name of Participant: _____
Date: _____
Place: _____
Signature or mark _____

Witnessed by:
Name of Witness: _____
Signature: _____
Date: _____

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

OBSTETRICS AND GYNAECOLOGY
School of Clinical Medicine

Rahima Moosa Mother and Child Hospital
Private Bag X20,
Newclare
2112
Enquiries: Prof H Lombaard
Tel: 011 470 9090/9096
21 July 2020

Ms Maumela
Post Graduate Office

Dear Ms Maumela

Re: Dr M Joomratee (MBChB)Student Number: 2294271

Title: A comparison of early onset preeclampsia and late onset preeclampsia

The **aim of the study** is to compare the maternal parameters and clinical presentations as well as the fetal and short term neonatal outcomes in early and late onset preeclampsia. My **supervisor** at RMMCH is Dr Wise.

Regards

Prof Hennie Lombaard
Adjunct Professor
Academic Head: Obstetrics and Gynecology
University of Witwatersrand
Head of Department: Obstetrics and Gynecology
Rahima Moosa Mother and Child Hospital
Tel.: 011 470 9090
Fax.: 011 470 9092

Appendix C

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

PERMISSION TO CONDUCT RESEARCH AT CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

PRINCIPAL RESEACHER:

FULL NAME: Moubiin JOOMRATEE

DESIGNATION: Medical Doctor

CONTACT NUMBER: 0649071744

EMAIL: moubiin.j@gmail.com

NAME OF SUPERVISOR: Professor Adam

TITLE OF RESEARCH : A Comparison of Early Onset Preeclampsia and Late Onset Preeclampsia

STUDY SITE/S: Chris Hani Baragwanath Academic Hospital

BRIEF OUTLINE OF METHODOLOGY :

A comparison of Early Onset Preeclampsia and Late onset Preeclampsia. Early and Late onset Preeclampsia have long been thought of as 2 separate pathologies The various physiological and pathological changes associated with both ought to be explored. The way they each affect the maternal and fetal physiologies and their short term impact on the newborn will be explored in this study

EXPECTED START DATE: August 2020

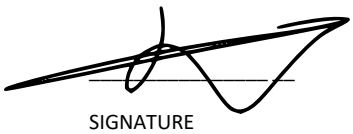
EXPECTED DURATION: About 10 months

ETHICS CLEARANCE? : PENDING APPROVAL FROM CEO

CONFLICT OF INTEREST? No

COST TO HOSPITAL AND OR PATIENTS? No

APPROVAL OF HOD: YES



Moubiin JOOMRATEE (MBChB) _____

SIGNATURE NAME IN PRINT+ DESIGNATION OFFICAL STAMP+ DATE

Appendix D

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

RAHIMA MOOSA MOTHER AND CHILD HOSPITAL

Enquiries : Karen Marshall
Tel : (011) 470 9284
Fax : 086 553 4623
Email : Karen.Marshall@wits.ac.za

TITLE OF RESEARCH PROJECT:
"A CPMPARISON OF EARLY ONSET PREECLAMPSIA AND LATE ONSET PREECLAMPSIA"

NAME OF SUPERVISOR:
Dr Amy Wise

NAME OF RESEARCHER:
Dr Moubiin Joomratee
Department of Obstetrics and Gynaecology
University of the Witwatersrand

NHRD REF NO: GP_202007_042

Dear Dr Joomratee,

Permission is granted for you to conduct the research as indicated in the title above.

The terms under which this permission is granted is contained in the Researcher Declaration form that you have signed. Failure to comply with these conditions will result in the withdrawal of such permission.

It is crucial for you to inform the Research Coordinator, Karen Marshall of the actual start and end dates of your study. This could be done by e-mail.

Should the study commence more than 12 months after receipt of this approval letter you will have to go through the process of applying again.

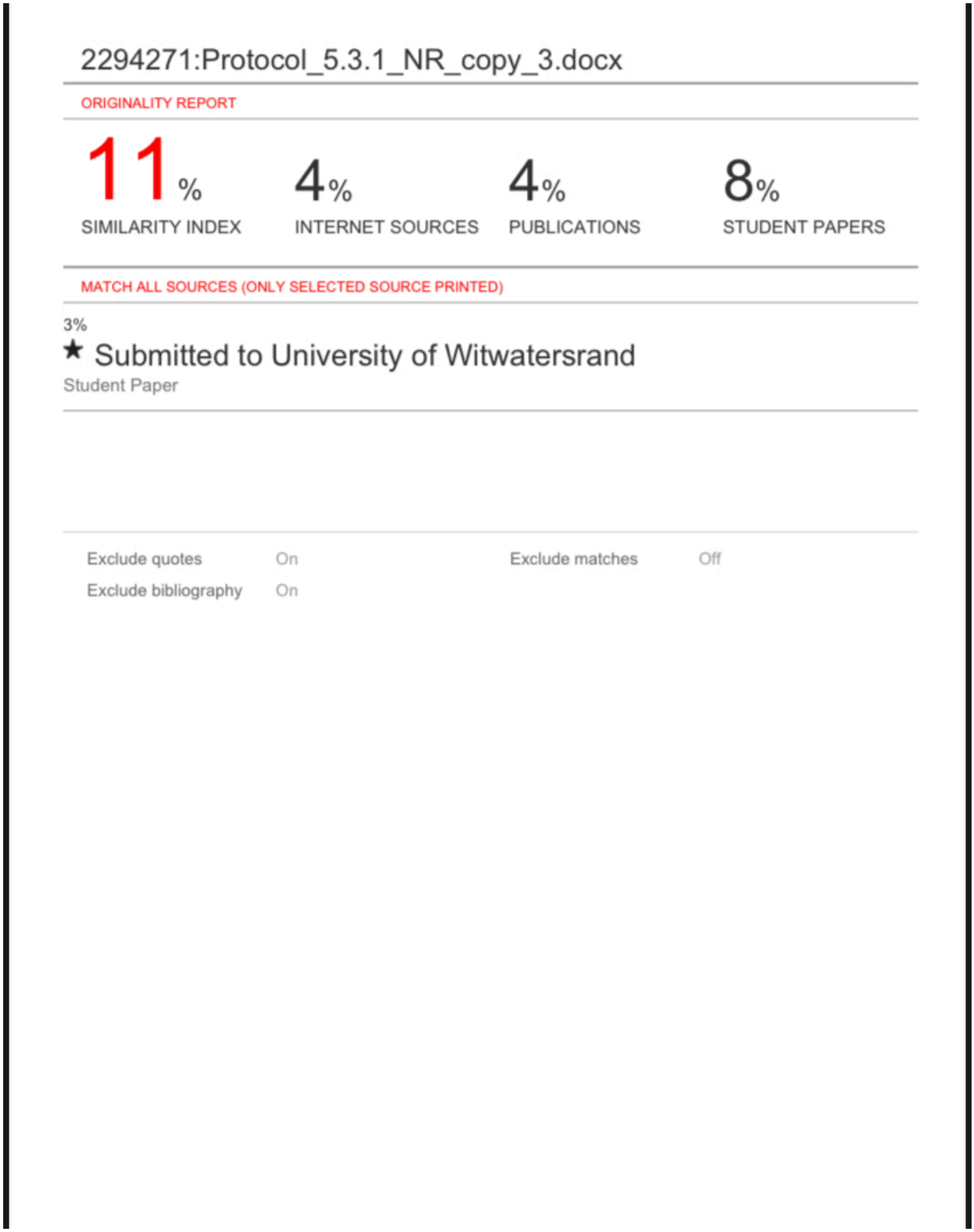
You are strongly advised to keep a signed copy of the declaration form to ensure that the terms of this agreement are always complied with.

Yours sincerely,

DR FREW BENSON
ACTING CHIEF EXECUTIVE OFFICER
2020:10:28

ADDRESS: Cnr FUEL & OUDSTHOORN STREET CORONATIONVILLE 2093 / PRIVATE BAG X20 NEWCLARE 2112 JHB

Appendix E



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Appendix F

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr Moubiin Moubarak Joomratee

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M200806

NAME: (Principal Investigator)	Dr Moubiin Moubarak Joomratee
DEPARTMENT:	Obstetrics and Gynaecology Chris Hani Baragwanath Academic Hospital Rahima Moosa Mother and Child Hospital
PROJECT TITLE:	A comparison of early onset preeclampsia and late onset preeclampsia
DATE CONSIDERED:	28/08/2020
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr A. Wise, Prof Y. Adam and Dr P. Naidoo
APPROVED BY:	CB Penny Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	06/11/2020

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions.Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report.** The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in **August** and will therefore be due in the month of **August** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

10th November 2020.
Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Author Guidelines according to IJGO

1. Submission

Authors must submit manuscripts online through IJGO's **Editorial Manager site (EM)**. If you are using EM for the first time, please click the 'Register' button at the top of the page and enter the requested information. If you are a returning user, please click the 'Login' button at the top of the page and enter your username and password. To submit a manuscript: please click the 'Submit a manuscript' button at the top of the page. Authors should send queries concerning the submission process or journal procedures to **ijgo@figo.org**.

There is no charge for submitting a paper to IJGO, and IJGO does not levy page charges or fees for publication of colour figures.

2. Authorship

Please ensure that you have each author's full name, email address, and affiliation ready when you submit your manuscript via EM, and that you have agreed who will act as the corresponding author. Only one corresponding author per manuscript is allowed; please ensure that the corresponding author listed in the manuscript is the same as the corresponding author listed in EM. All named authors must fulfil **ICMJE authorship criteria**. Any contributors who do not fulfil all ICMJE criteria, including those involved solely in data collection, should be recognized separately in the Acknowledgment(s) section.

Research from individual low- and middle-income countries must include local co-authors and collaborators. These research and academic colleagues should be identified early and should meet the ICMJE authorship criteria. Principles of community-based participatory research should be strongly considered. This supports FIGO priorities for capacity-building and prevents any perception that data or research is being co-opted by scholars from high-income countries. Multi-country studies or analyses of internationally available databases do not necessarily have to meet this requirement.

3. Peer review process

Once submitted, manuscripts undergo initial screening by the editorial office and Editors. To ensure timely processing of the large number of submissions received, papers that do not meet the journal's submission requirements, standards, scope, or are not seen to be sufficiently novel will be rejected without peer review, and the authors will receive prompt notification.

The submitting author can check the status of their manuscript during the review process by logging into EM; any co-authors should contact the submitting author for status updates. All communication, including notification of the editor's decision and requests for revision, is via email to the corresponding author’s email address as listed in EM.

The IJGO peer review process is single-blinded (i.e. the authors’ names are not anonymised prior to peer review, but reviewer names are anonymised when

returning reviewer comments to authors).

4. Cover letter

All submissions, other than Correspondence, must include a cover letter. This should be addressed to the Editor-in-Chief, and should include the following:

- A statement that the paper is not currently published or under consideration elsewhere.
- Details of whether the paper has previously been submitted to another journal. If it has previously been submitted elsewhere, please state which journal(s), and whether you consent to share the reviewers' feedback (if any). Previous reviewer feedback should be uploaded using the file type 'Miscellaneous'. IJGO's peer review process is independent of any previous evaluation by other journals, but providing this feedback may help to expedite the decision process.
- If more than 6 authors listed on the manuscript, an explanation of how all authors meet **ICMJE criteria for authorship**.
- Word count.
- Conflicts of interest for any of the authors.
- If copyright permission is required to reproduce any material in an article (e.g. figures or tables that have previously been published elsewhere), include confirmation that permission has been obtained from the copyright holder (see 6.5. Figures).

5. Article types

5.1. Clinical articles

For information on clinical trials, please also see section **5.1.1. Clinical trials** below.

Observational studies in epidemiology (cohort, case-control, and cross-sectional studies) should follow the STROBE statement and checklist.

Clinical Articles should discuss original research, and must include the following elements:

- **Title**

The title of the manuscript should include the subtitle 'Randomized controlled trial' or 'Clinical trial'.

- **Authors**
    - Primary research studies carried out in **low-/middle-income countries** must have at least one local co-author.
- **Author affiliations**
    - Please list department, institution, city, country only.
- **Corresponding author info**
    - Only one corresponding author should be listed. The corresponding author listed in the manuscript file must match the corresponding author listed in Editorial Manager.
    - Full postal address and email address should be listed.
- **Structured abstract**

- Headings: Objective; Methods; Results; and Conclusion.
- Guideline word count: Up to 250 words.

- **Keywords**
  - Guideline: Up to 8 keywords. At least 3 keywords must be included.

- **Synopsis**
  - Brief synopsis of up to 25 words describing the key findings of the study.

- **Main text**
  - Guideline word count: Up to 2500 words
  - Continuous line numbering used throughout
  - Citations: in-text references listed using Arabic numerals in square brackets (e.g. [1,2]), OR using superscript reference indicators (e.g. [1,2]). Do not use parentheses (curved brackets).
  - No footnotes
  - Main headings:
    - *Introduction*
      - Present the background to the study briefly, supported by a limited number of references. State the rationale for the study, and include the study objectives and hypothesis at the end of this section.
    - *Materials and methods*
      - State the type of study at the beginning of this section (e.g., retrospective cohort study).
      - Describe concisely the study setting, dates (day, month and year), participants, methods and procedures, and statistical methods. Where appropriate, state the program

used for statistical analysis (including model and version number), and the cut-off for statistical significance. This section should include sufficient detail to allow others to replicate the study.

- For studies of patients, patient records, or volunteers, include a statement of**prospective** local Ethics Committee approval (including full name of Committee).
- For studies with human participants, include a statement about informed consent. If consent was not needed/obtained, include an explanation. Authors must provide copies of the appropriate documentation if requested.

- *Results*
  - Include the outcome of the study and statistical significance, if appropriate.
  - Tables and figures should be cited here in order, to illustrate the outcomes and supplement the text.
- *Discussion*
  - Discuss the relevance of the results. Compare with previously published studies; discuss strengths and limitations of the study; address any proposals for future research where relevant.
- *Conclusions*
  - Discussion and Conclusions sections may be formatted as one section as preferred.

        - Briefly state the key findings of the study, and major implications for clinical practice/research where relevant.
- **Author contributions:** List each author's role in the design, planning, conduct, data analysis, and manuscript writing. Ensure that all authors meet the **ICMJE criteria for authorship** (anyone who does not fulfil all four criteria should be moved to an Acknowledgments section).
- **Funding:** All sources of funding received for the research, authorship, and/or publication of the article must be listed here. This should match any funding sources listed in Editorial Manager. If no funding was received for the research, state 'None'.
- **Conflict of interest:** List any relationships that may be deemed COIs, or state 'The authors have no conflicts of interest'.
- **References:** See **6.3. References** for reference style. Guideline: up to 25 references.
- **Figures and tables:** See Figures and Tables sections below for further information.

5.1.1. Clinical trials

The ICMJE defines a clinical trial as "any research project that prospectively assigns people or a group of people to an intervention, with or without concurrent comparison or control groups, to study the cause-and-effect relationship between a health-related intervention and a health outcome."

When reporting a clinical trial, authors should consult the **CONSORT statement and checklist**.

Authors must be prepared to share their anonymised data sets for the purposes of peer review if requested to do so by the Editorial Board. Anonymised data sets may be reviewed by our Research Integrity Editor or Statistical Consultant, and will not be held on file following peer review.

Follow the instructions for clinical articles as above, but in addition all clinical trials **must** include all of the following elements. **If any of these items are not present, the submission will immediately be returned to the corresponding author for revision, or rejected**.

- All clinical trials **must** be registered in a public trials registry to be considered for publication. Registration must be **prospective**, i.e. the registration date must be before or on the same date as enrolment of the first patient.

Suggested registries can be found here: **http://www.who.int/ictrp/network/primary/en/**.

Include the following elements:

Abstract

- Name of the registry
- Registration number
- URL of registration: this must link directly to the individual record for your paper on the trial registry (**not** to the registry homepage).

Materials and methods

- **CONSORT flow diagram** must be cited here, and uploaded as a figure file
- Statement of adherence to CONSORT Guidelines
- The following details must be included, and should match those given in the trial registry:
    - Full dates of study (day, month, year)
    - Setting of study (including full names of institutions)
    - Full name of approving Ethics Committee
    - Reference ID of ethical approval
    - Details of power calculation: provide the power of the study, and state how the power calculation was determined, including what type of difference the calculation was powered to detect and on what studies the numbers are based
    - Recruitment numbers
    - Participant dropout rate.
- Type of statistical analysis
- The patient information leaflet and patient consent form (template) should be uploaded as supplementary files where available (see **6. Supporting information**).

5.2 Systematic reviews and meta-analyses

Systematic reviews and meta-analyses should follow the PRISMA guidelines. All submitted systematic reviews and meta-analyses undergo initial review by IJGO's Systematic Reviews Editor.

Systematic reviews **must** include:

- Detailed risk of bias assessments for the individual studies in table format (these assessments should be substantiated with any relevant text from the original studies)
- The line-by-line search strategies for each of the different bibliographic databases
- A completed **PRISMA Checklist**.

Meta-analyses of observational studies must follow **MOOSE guidelines**. Meta-analysis may be contained within a systematic review.

IJGO endorses the use of the **GRADE system** for grading evidence when recommendations are made as a result of a systematic review.

Include the following elements:

- **Title**
- **Authors**
- **Author affiliations**
    - Please list department, institution, city, country only.
- **Corresponding author info**
    - Only one corresponding author should be listed. The corresponding author listed in the manuscript file must match the corresponding author listed in Editorial Manager.
    - Full postal address and email address should be listed.
- **Abstract**

Structured abstract with the following headings:

-
  - Background
  - Objectives
  - Search strategy
  - Selection criteria
  - Data collection and analysis
  - Main results
  - Conclusions

- **Keywords**
  - Guideline: Up to 8 keywords. At least 3 keywords must be included.
- **Synopsis**
  - Brief synopsis of up to 25 words describing the key findings of the study.
- **Main text**
  - Guideline word count: Up to 4000 words
  - Continuous line numbering used throughout
  - Citations: in-text references listed using Arabic numerals in square brackets (e.g. [1,2]), OR using superscript reference indicators (e.g. ^{1,2}). Do not use parentheses (curved brackets).
  - No footnotes
  - Main headings:
    - Introduction

Describe the background and rationale for the review.

-
    - Objectives
    - Methods
        - Eligibility criteria, information sources, search strategy
            - Include line-by-line search strategies for each of the different bibliographic databases
            - Study selection
            - Data extraction
            - Assessment of risk of bias
            - Data synthesis

- **Results**
    - Study selection
    - Study characteristics
    - Risk of bias of included studies
    - Risk of bias for individual studies should be included in table format, substantiated with relevant text from the original studies
    - Synthesis of results

- Conclusions
    - Comparison with existing literature
    - Strengths and limitations
    - Implications
    - Supplemental material: Upload a completed PRISMA checklist.
- **Author contributions:** List each author's role in the design, planning, conduct, data analysis, and manuscript writing. Ensure that all authors meet the **ICMJE**

criteria for authorship (anyone who does not fulfil all four criteria should be moved to an Acknowledgments section).

- **Funding:** All sources of funding received for the research, authorship, and/or publication of the article must be listed here. This should match any funding sources listed in Editorial Manager. If no funding was received for the research, state 'None'.
- **Conflict of interest:** List any relationships that may be deemed COIs, or state 'The authors have no conflicts of interest'.
- **References:** See **6.3. References** for reference style. Guideline: up to 80 references.
- **Figures and tables: 6.4. Tables** and **6.5. Figures** for further information.

5.3. Narrative reviews

Narrative review articles should discuss and synthesize the key, recent, peer-reviewed literature on the topic, and should aim to be as comprehensive and balanced as possible. Narrative reviews may contain recommendations and guidance for practice.

Include the following elements:

- **Title**
- **Authors**
- **Author affiliations**
    - Please list department, institution, city, country only.
- **Corresponding author info**

- Only one corresponding author should be listed. The corresponding author listed in the manuscript file must match the corresponding author listed in Editorial Manager.
- Full postal address and email address should be listed.

- **Abstract**

Include an unstructured abstract. Guideline word count: Up to 250 words.

- **Keywords**
  - Guideline: Up to 8 keywords. At least 3 keywords must be included.
- **Synopsis**
  - Brief synopsis of up to 25 words describing the key findings of the study.
- **Main text**
  - Guideline word count: Up to 4000 words
  - Continuous line numbering used throughout
  - Citations: in-text references listed using Arabic numerals in square brackets (e.g. [1,2]), OR using superscript reference indicators (e.g. ^{1,2}). Do not use parentheses (curved brackets).
  - No footnotes
  - Headings and subheadings as appropriate for the topic
- **Author contributions:** List each author's role in the design, planning, conduct, data analysis, and manuscript writing. Ensure that all authors meet the **ICMJE criteria for authorship** (anyone who does not fulfil all four criteria should be moved to an Acknowledgments section).
- **Funding:** All sources of funding received for the research, authorship, and/or publication of the article must be listed here. This should match any funding

sources listed in Editorial Manager. If no funding was received for the research, state ‘None’.

- **Conflict of interest:** List any relationships that may be deemed COIs, or state ‘The authors have no conflicts of interest’.
- **References:** See **6.3. References** for reference style. Guideline: up to 25 references.
- **Figures and tables:** See **6.4. Tables** and **6.5. Figures** for further information.

5.4. Brief communications

Brief communications comprise case reports or short summaries of original research. All case reports should be submitted as the article type ‘Brief Communication’. Include the following elements:

- **Title**
- **Authors**
- **Author affiliations**
    - Please list department, institution, city, country only.
- **Corresponding author info**
    - Only one corresponding author should be listed. The corresponding author listed in the manuscript file must match the corresponding author listed in Editorial Manager.
    - Full postal address and email address should be listed.
- **No abstract**
- **Keywords**
    - Guideline: Up to 8 keywords. At least 3 keywords must be included.
- **Synopsis**

- Brief synopsis of up to 25 words describing the key findings of the study.

- **Main text**
  - Guideline: Up to 400 words. **Brief communications have a strict upper limit of 800 words.**
  - Continuous line numbering used throughout.
  - Citations: in-text references listed using Arabic numerals in square brackets (e.g. [1,2]), OR using superscript reference indicators (e.g. [1,2]). Do not use parentheses (curved brackets).
  - No footnotes
  - No headings
  - For case reports, **ethical approval and patient consent must be mentioned** in the main text.
- **Author contributions:** List each author's role in the design, planning, conduct, data analysis, and manuscript writing. Ensure that all authors meet the **ICMJE criteria for authorship** (anyone who does not fulfil all four criteria should be moved to an Acknowledgments section).
- **Funding:** All sources of funding received for the research, authorship, and/or publication of the article must be listed here. This should match any funding sources listed in Editorial Manager. If no funding was received for the research, state 'None'.
- **Conflict of interest:** List any relationships that may be deemed COIs, or state 'The authors have no conflicts of interest'.
- **References:** See **6.3. References** for reference style. Guideline: up to 4 references. **Brief Communications have a strict upper limit of 8 references.**

- **Figures and tables:** See **6.4. Tables** and **6.5. Figures** for further information. **Brief Communications have a strict upper limit of 1 table or 1 figure** (if additional figures/tables are essential to understanding, these may be uploaded as supplementary material).

5.5. Case report and literature review

IJGO accepts a small number each year of case reports including more extensive literature review. These manuscripts should be submitted as the article type 'Narrative Review', and the title of the paper should mention that it is a case report and literature review.

Include the following elements:

- **Title**
- **Authors**
- **Author affiliations**
    - Please list department, institution, city, country only.
- **Corresponding author info**
    - Only one corresponding author should be listed. The corresponding author listed in the manuscript file must match the corresponding author listed in Editorial Manager.
    - Full postal address and email address should be listed.
- **Abstract**

Include an unstructured abstract. Guideline word count: Up to 250 words.

- **Keywords**

- Guideline: Up to 8 keywords. At least 3 keywords must be included.

- **Synopsis**
  - Brief synopsis of up to 25 words describing the key findings of the study.

- **Main text**
  - Guideline word count: Up to 3000 words
  - Continuous line numbering used throughout
  - Citations: in-text references listed using Arabic numerals in square brackets (e.g. [1,2]), OR using superscript reference indicators (e.g. [1,2]). Do not use parentheses (curved brackets).
  - No footnotes
  - Headings and subheadings as appropriate for the topic
  - For the case report element, **ethical approval and patient consent must be mentioned i**n the main text

- **Author contributions:** List each author's role in the design, planning, conduct, data analysis, and manuscript writing. Ensure that all authors meet the **ICMJE criteria for authorship** (anyone who does not fulfil all four criteria should be moved to an Acknowledgments section).
- **Funding:** All sources of funding received for the research, authorship, and/or publication of the article must be listed here. This should match any funding sources listed in Editorial Manager. If no funding was received for the research, state 'None'.
- **Conflict of interest:** List any relationships that may be deemed COIs, or state 'The authors have no conflicts of interest'.
- **References:** See **6.3. References** for reference style. Guideline: up to 25 references.

Figures and tables: See **6.4. Tables** and **6.5. Figures** for further information.

5.6. Correspondence

IJGO accepts Letters to the Editor that discuss one or more article published in IJGO within the past year. These do not undergo full peer review, but may be accepted for publication at the Editor-in-Chief's discretion. A response from the authors of the original article will be invited by the editorial office, and should a response be submitted, the two pieces will be published in tandem.

Include the following elements:

- **Title**
- **Authors**
- **Author affiliations**

Please list department, institution, city, country only.

- **Corresponding author info**
    -
    - Only one corresponding author should be listed. The corresponding author listed in the manuscript file must match the corresponding author listed in Editorial Manager.
    - Full postal address and email address should be listed.
- **Main text**
    -
    - Guideline word count: Up to 800 words

- Continuous line numbering used throughout
- Citations: in-text references listed using Arabic numerals in square brackets (e.g. [1,2]), OR using superscript reference indicators (e.g. [1,2]). Do not use parentheses (curved brackets).
- No footnotes
- No headings

- **Conflict of interest:** List any relationships that may be deemed COIs, or state 'The authors have no conflicts of interest'.
- **References:** See **6.3. References** for reference style. Guideline: up to 10 references. The original article under discussion should be listed as the first reference.

6. Editorial style

6.1. Language

Papers are published in English, using US spelling. Authors are strongly encouraged to use neutral, unbiased language that respects women's bodies and agency. The editors reserve the right to make any necessary editorial changes.

Authors whose first language is not English are encouraged to have their manuscripts reviewed by a native English speaker or a professional editing service before submission, e.g. **http://wileyeditingservices.com/en/**. It is important for all submissions to be clear and coherent for the editors and reviewers.

6.2. File types

Papers should be submitted as Word documents, formatted in Arial 12pt with double line spacing. For information on accepted file types for figures and tables, please see **6.4. Tables** and **6.5. Figures**.

6.3. References

IJGO uses a modified Vancouver style of referencing; i.e. references must be numbered and listed as they are cited in the article, using Index Medicus abbreviations for journal titles (e.g. *Int J Gynecol Obstet*). Most references should be dated within the past 10 years.

Cite the names of all authors when there are six or fewer; when there are seven or more, list the first three authors followed by “et al.” Include the volume number.

Journal article

[1] Vellacott ID, Cooke EJ, James CE. Nausea and vomiting in early pregnancy. *Int J Gynecol Obstet*1988;27:57–59.

Book

[2] Speroff L, Glass BH, Kase NG. *Clinical Gynecologic Endocrinology and Infertility*. Baltimore: Williams and Wilkins; 1982.

Chapter in a book

[3] Disaia PJ, Creasman WT. Invasive Cancer of the Vulva. In: Disaia PJ, Creasman WT, eds. *Clinical Gynecologic Oncology*. St Louis: C.V. Mosby; 1984:214–219.

Web reference

[4] World Health Organization. WHO Recommended Surveillance Standards, Second Edition [WHO website]. 1999. http://www.who.int/csr/resources/publications/surveillance/whocdscsrisr992.pdf. Accessed January 15, 2016.

Text references should be indicated by Arabic numerals in square brackets on the line; for example, [1–4] and [1,5,11,17]. Alternatively, they may be indicated using superscript numbering. Please ensure whichever method is used, that it is used consistently throughout. To avoid any delays in the editing process, authors must make every effort to ensure that each reference is correct and complete.

All references must be in English. Citation information of documents originally in other languages must be translated into English in the reference list.

Numbered references to personal communications, unpublished data, statistical software, or manuscripts that have not been accepted for publication (i.e. "submitted" or "under consideration") must not be included. Reference to such material, if required, can be incorporated at the relevant location in the text.

If bibliographic software has been used for managing the reference list (e.g. EndNote or Reference Manager), the reference list and citations must be unlinked before submission.

When citing articles available as preprints, which have not yet been published, the designation “[preprint]” should be included in the reference.

6.4. Tables

- Tables must be titled, numbered consecutively, and cited in the text as ‘Table 1’, ‘Table 2’, etc. All tables must be created and submitted in editable Word format.
- Use the Word table function (not the "enter" key, spaces, or the "tab" function) to create a separate cell for each table entry.
- Footnotes to tables should be listed as a,b,c etc., rather than *,†,‡ etc.
- If tables are deemed to be too large or there are too many, they may be published as online-only **supporting information**.

6.5. Figures

- Upload figures individually, in separate files (one figure per file). **Do not embed the figure into the main manuscript file**.
- Preferred image formats are TIFF, JPEG, or EPS (at least 300 dpi).
- Upload CONSORT flow charts as editable Word/PowerPoint files.
- For every figure, provide a short figure title (numbered consecutively in the order of citation, using Arabic numerals) in the manuscript file, following the reference list.
- Cite all figures in numeric order in the main text as "Figure 1" etc.
- There are no charges for color figures.
- If photographs of identifiable people are used, authors must obtain and submit a signed statement of informed consent from the identifiable person(s) or their

next of kin. Authors should not try to conceal identity with black bars over eyes etc.

- If any figures have previously been published elsewhere, excluding those published open access under a CC-BY licence, authors must first obtain the permission of the copyright holder, in addition to giving precise reference to the original work. Confirmation should be included in the cover letter (the actual permission correspondence from the copyright holder does not need to be submitted).

6.6. Supporting information (Supplementary files)

- Authors may submit supporting information such as additional tables and figures, presentations, and videos.
- These should be uploaded as file type 'Supplementary file', and cited in the main manuscript file as "Table S1", "Figure S1", "Video S1", etc.
- Supporting information will be hosted online only.
- Supporting information will not be edited or formatted, but the editors and reviewers may suggest changes.

6.7. Statistics and reporting of numbers

6.7.1. Statistics

The statistical tests used and the significance level set should be listed in the methods for all studies that employ statistical analysis. Include information regarding the statistical software programs used in the Methods section; for example, "SPSS version 20 (IBM, Armonk, NY, USA)."

P values should be provided where calculated. The largest *P* value that should be expressed is *P* > 0.99. The smallest P value that should be expressed is *P* < 0.001.

For measures of effect (e.g. relative risks, risk ratios, odds ratios), authors should also report confidence intervals (e.g. 95% CI) so that the precision of the effect estimate can be assessed.

6.7.2. Numbers

Use Arabic numerals for weights, measures, percentages, and degrees of temperature. Weights and measures should be abbreviated according to the International System of Units (SI) or non-SI units mentioned in the SI, followed by conventional units in brackets on first mention. Provide percentages after numerals when reporting results.

6.8. Drugs

Give generic names of all pharmaceutical preparations and, where appropriate, include the trade name and manufacturer's name and address in parentheses. Review drug names and dosages with care. The author is responsible for all recommended dosages.

6.9. Manufacturer information

Give the manufacturer's name and address in parentheses following the name of any instruments or equipment cited by brand name. Do not include the trademark or registered trademark symbol.

7. Open Access

IJGO is a ‘hybrid’ journal – i.e. it is a subscription-based journal, but some authors may choose to publish their article Open Access, whereby it will be immediately and permanently free for everyone to read and download. There is no charge to authors or their institutions for subscription-based publication.

- To cover the cost of publishing Open Access, authors or their institutions pay an article publication charge (APC). The APC for IJGO can be found on Wiley’s **Open Access Pricing page**.
- Payment must be received before the article can be made open access. Some organizations pay APCs for their authors via a **Wiley Open Access Account**.
- Visit Wiley’s **Open Access page** for more information and instructions on how to order.

7.1. Benefits of Open Access

- The article is made freely available to all (not just to IJGO subscribers).
- Authors can post the final, published PDF of their article on a website, institutional repository, or other free public server
- Articles will be automatically submitted to PubMed Central and PMC mirror sites, when appropriate
- Authors retain copyright with a Creative Commons license
- Authors can fully comply with funder open access mandates

7.2. Copyright, Open Access licenses and funder compliance

Authors choosing Open Access will retain copyright in their articles and can choose between a range of licence types: see further information on **Wiley's licensing page**.

Not sure about your institution or funding agency open access policy? Find out with Wiley's **Author Compliance Tool**.

7.3. Green Open Access: Self-archiving

Green Open Access, also called self-archiving, is when the author, institution, or publisher places a version of the article online in a repository or website after publishing in a subscription-based journal – making it freely available to everyone. For more information about Wiley's policy, visit the **Self-Archiving page**.

7.4. Referrals to Reproductive, Female and Child Health

If your manuscript is not accepted for publication in IJGO, your manuscript may be suitable for submission to the Wiley-published journal, ***Reproductive, Female and Child Health*** (RFCH). RFCH is a peer-reviewed, multi-disciplinary, Gold Open Access journal, which aims to improve clinical practice in reproductive, female, and child health.

If your manuscript is considered suitable for submission to RFCH, you will receive a decision email from the IJGO Editor with the opportunity to complete a form to transfer your manuscript to RFCH's submission site. Please note that submission to RFCH does not guarantee acceptance of your manuscript, and please note that, as

a fully Gold Open Access journal, an Article Publication Charge is required for publication in RFCH.

8. Policies

8.1. Data-sharing policy

This journal expects data sharing for Clinical Articles, and authors must include a data availability statement. Review **Wiley's Data Sharing policy** where you will be able to see and select the data availability statement that is right for your submission. Brief Communications, Review Articles and Editorials do not need a data availability statement, but may include one if relevant.

8.2. Appeals

- An author may appeal a Reject decision within 30 days of receipt of the decision email.
- Appeals will be considered only if factual errors are believed to have been made during the review process.
- Only one appeal is permitted per manuscript, and decisions on appeals are final.
- The basis for an appeal must be outlined clearly; the corresponding author should email the IJGO Editorial Office at ijgo@figo.org.

8.3. Plagiarism

Plagiarism entails the "use or close imitation of the language and thoughts of another author and the representation of them as one's own original work." Self-plagiarism, a form of misconduct in which an author reuses his/her previously written text, data, or

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