# Seasonal variation in preeclampsia –
# Timing of conception vs timing of delivery

by

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# Declaration

I, the undersigned, hereby declare that the work contained in this thesis is my own original work and that I have not previously in its entirety or in part, submitted it at any university for a degree.

_____
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31/03/2012
Date

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# Abstract


## Season variation in preeclampsia – timing of delivery vs timing of conception

### Background

Preeclampsia is a multi-system disease characterized by hypertension and proteinuria in pregnant women at greater than 20 weeks of gestational age. It remains one of the leading causes of maternal and foetal mortality and morbidity.

While the cause of preeclampsia is essentially unknown, the important theories strongly implicate disturbed placental function in early pregnancy. Additionally, some researchers have investigated the possibility of a seasonal relationship with the incidence of preeclampsia. Differences in incidences of preeclampsia, examined exclusively on the basis of delivery timing, have also been noted to have seasonal variation, but results have been inconsistent.

### Objective

Our primary objective was to investigate the seasonal variation in preeclampsia in relation to the timing of conception and the timing of presentation with clinical disease over the period of one year.

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**Methods**

We performed a retrospective descriptive study of all women with preeclampsia who delivered at Tygerberg Hospital in 2010. Preeclampsia was diagnosed as hypertension associated with proteinuria after the 20th week of gestation.
Names of patients were identified from labour ward records and data was collected and recorded on a data-sheet.

Data were primarily analysed in relation to the season of delivery and also the season of the last menstruation. Summer was diagnosed as lasting from summer solstice to autumn equinox, autumn as lasting from autumn equinox until winter solstice, winter as lasting from winter solstice until spring equinox and spring as lasting from spring equinox until summer solstice.

The data was analysed using the SPSS software (Statistical Package for Social Science). Discrete data was compared by calculating relative risks with 95% confidence limits, as well as the $chi^2$ test. Fisher's exact test was used to compare ratios where the expected value in any cell of a two-by-two table is less than five. The means of normally distributed continuous data was compared by analysis of variance, while the medians of continuous data which are not distributed normally, where calculated using the non-parametric Mann Whitney u test. A p-value of $< 0.05$ was considered to be statistically significant, where applicable.

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**Results**

The peak incidence of preeclampsia was during winter with 32.2% of all cases occurring during this season. This was significantly higher than during the summer when only 169 (17.17%) cases of preeclampsia were delivered.

When we analysed the data looking at the timing of menstruation (and therefore conception), we found that 292 (29.7%) patients that developed preeclampsia had their last menstrual period in the spring, with November the month of peak incidence. The lowest incidence was found in winter, with only 218 (22.2%) patients.

**Conclusion**

We have confirmed a previous finding of a seasonal variation in the occurence of preeclampsia in Tygerberg Hospital. We have also confirmed that this seasonal variation is not only influenced by the timing of delivery, but also by the timing of conception.

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# Introduction

Preeclampsia is a multi-system disease characterized by de novo hypertension and significant proteinuria in pregnant women at greater than 20 weeks of gestational age.[1]

Clinically, this disease can be classified as 'severe' when severe hypertension, severe proteinuria, or other signs or symptoms of end-organ injury are present.[2,3] In the absence of any of these findings, preeclampsia can be classified as 'mild'. In this commonly used system, there is no 'moderate' classification.

Globally, preeclampsia occurs in up to 7.5 percent of pregnancies.[4,5] It remains one of the leading causes of maternal, fetal and neonatal morbidity and mortality – accounting for 10 – 15 percent of direct maternal deaths worldwide.[6]

Maternal morbidity includes the development of eclamptic convulsions, HELLP-syndrome (haemolysis, elevated liver enzymes, low platelets), pulmonary oedema, abruptio placentae and temporary loss of vision – either through PRES-syndrome (posterior reversible encephalopathy) or serous retinal detachment. In more severe cases, the patient can develop acute renal and liver failure. If these complications are not appropriately managed, the patient's condition will deteriorate into multisystem organ failure and even death. Acute severe systolic hypertension (systolic pressure greater than 160mmHg) is also associated with an increased risk of intra-cerebral haemorrhage.

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The fetal complications include intra-uterine growth restriction, placental insufficiency and even intra-uterine death. Because of the intra-uterine growth restriction and placental insufficiency, there is also an increase in the rate of deliveries by caesarean section – again increasing maternal and neonatal morbidity.

The neonatal complications include hyaline membrane disease, NEC (necrotizing enterocolitis) and intra-ventricular haemorrhage. The neonatal complications are all due to prematurity – usually secondary to a worsening maternal condition necessitating delivery well before 34 weeks. Though the use of antenatal steroids and expectant management has greatly improved the outcome for neonates, especially in larger centres, morbidity and mortality remain high and a great financial burden on any health system.

While the cause of preeclampsia is essentially unknown, the pathophysiology likely involves both maternal and fetal or placental factors. Abnormalities in the development of placental vasculature early in pregnancy may result in relative placental hypoperfusion and hypoxia –even ischaemia - which then leads to release of antiangiogenic factors into the maternal circulation that alter maternal systemic endothelial function and cause hypertension and other manifestations of the disease. However, the molecular basis for placental dysregulation of these pathogenic factors remains unknown, and the role of angiogenic proteins in early placental vascular development are under investigation.

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The critical role of the placenta in the pathophysiology of preeclampsia is supported by epidemiologic and experimental data that show two things. Firstly, placental tissue is necessary for development of the disease, but the fetus is not. Secondly, preeclampsia is always cured after delivery of the placenta.

Examination of human placentas at various stages of gestation in women with normal pregnancies, as well as those with preeclampsia, has led to an understanding of normal placental morphology and pathologic changes in the uteroplacental circulation that are likely to be relevant to preeclampsia.

**Abnormal remodeling of spiral arteries** — In normal pregnancies, the cytotrophoblast cells of the developing placenta migrate through the decidua and part of the myometrium to invade both the endothelium and highly muscular tunica media of the maternal spiral arteries, the terminal branches of the uterine artery that supply blood to the developing fetus/placenta. As a result, these vessels undergo transformation from small muscular arterioles to large capacitance vessels of low resistance, thus greatly facilitating blood flow to the placenta compared with other areas of the uterus.[7,8] Remodeling of the spiral arteries probably begins in the late first trimester and is completed by 18 to 20 weeks of gestation, although the exact gestational age at which trophoblast invasion of these arteries ceases is unclear.

By comparison, in preeclampsia, cytotrophoblast cells infiltrate the decidual portion of the spiral arteries, but fail to penetrate the myometrial segment.[9,10] The spiral arteries fail to develop into large, tortuous vascular channels created by replacement

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of the musculoelastic wall with fibrinoid material; instead, the vessels remain narrow, resulting in placental hypoperfusion. This defect in deep placentation has been associated with development of multiple adverse pregnancy outcomes, including second trimester fetal death, placental infarcts, abruptio placentae, preeclampsia with or without intrauterine growth restriction, intrauterine growth restriction without maternal hypertension, premature rupture of membranes, and preterm labor.[11]

It is not known why the normal sequence of events in development of the uteroplacental circulation does not occur in some pregnancies. Vascular, environmental, immunological, and genetic factors all appear to play a role.[12]

**Defective trophoblast differentiation** — Defective differentiation of trophoblast is one possible mechanism responsible for defective trophoblast invasion of the spiral arteries.[13] Trophoblast differentiation during endothelial invasion involves alteration in expression of a number of different classes of molecules, including cytokines, adhesion molecules, extracellular matrix molecules, metalloproteinases, and the class Ib major histocompatibility complex molecule, HLA-G.[14,15] During normal differentiation, invading trophoblasts alter their adhesion molecule expression from those that are characteristic of epithelial cells (integrin alpha6/beta1, alphav/beta5, and E-cadherin) to those of endothelial cells (integrin alpha1/beta1, alphav/beta3, and VE-cadherin), a process referred to as pseudo-vasculogenesis[7]. Trophoblasts obtained from women with preeclampsia do not show upregulated adhesion molecule expression or pseudo-vasculogenesis. The resulting impaired placentation and accompanying ischemia are thought to be the primary events leading to placental

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release of soluble factors that cause systemic endothelial dysfunction resulting in the preeclamptic phenotype.

**HYPOPERFUSION, HYPOXIA, ISCHEMIA** — Hypoperfusion appears to be both a cause and a consequence of abnormal placental development. Hypoperfusion becomes more pronounced as pregnancy progresses since the abnormal uterine vasculature is unable to accommodate the normal rise in blood flow to the fetus/placenta with increasing gestational age[16-18]. Late placental changes consistent with ischemia include atherosis (lipid-laden cells in the wall of the arteriole), fibrinoid necrosis, thrombosis, sclerotic narrowing of arterioles, and placental infarction.[7,16,17,19,20,21] Although all of these lesions are not uniformly found in patients with preeclampsia, there appears to be a correlation between the severity of the disease and the extent of the lesions.[22,23]

Hypoperfusion, hypoxia, and ischemia is a critical component in the pathogenesis of preeclampsia because the hypoperfused, ischaemic placenta elaborates a variety of factors into the maternal bloodstream that alter maternal endothelial cell function and lead to the characteristic systemic signs and symptoms of preeclampsia.[24-30]

**IMMUNOLOGIC FACTORS** — The focus on immunologic factors as a possible contributor to abnormal placental development was based, in part, upon the observation that prior exposure to paternal/fetal antigens appears to protect against preeclampsia[31-37]. Nulliparous women and women who change partners between pregnancies, have long interpregnancy intervals, use barrier contraception, and

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conceive via intracytoplasmic sperm injection have less exposure to paternal antigens and higher risks of developing preeclampsia.

Immunologic abnormalities, similar to those observed in organ rejection graft versus host disease, have been observed in preeclamptic women.[38] The extravillous trophoblast (EVT) cells express an unusual combination of HLA class I antigens: HLA-C, HLA-E, and HLA-G. Natural killer (NK) cells that express a variety of receptors (CD94, KIR, and ILT) known to recognize class I molecules infiltrate the maternal decidua in close contact with the EVT cells.[39] Interaction between NK cells and EVT cells has been hypothesized to control placental implantation. In preeclampsia, conflict between maternal and paternal genes is believed to induce abnormal placental implantation through increased NK cell activity.

Placental bed biopsies from women with preeclampsia have revealed increased dendritic cell infiltration in preeclamptic decidual tissue.[40] The dendritic cells are an important initiator of antigen-specific T-cell responses to transplantation antigens. It is possible that increased number of dendritic cells may result in alteration in presentation of maternal and fetal antigens at the decidual level, leading to either abnormal implantation or altered maternal immunologic response to fetal antigens.

However, definitive evidence for this theory is lacking. A systematic review found no clear evidence that one or several specific HLA alleles were involved in the pathogenesis of preeclampsia.[42] Therefor, it has been suggested that interaction between maternal, paternal, and fetal HLA types, rather than any individual genotype

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alone, was probably an important factor to consider when studying immunogenetic determinants of preeclampsia.

A more promising finding is that patients with preeclampsia have increased levels of agonistic antibodies to the angiotensin AT-1 receptor. This antibody can mobilize intracellular free calcium and may account for increased plasminogen activator 1 production and shallow trophoblast invasion seen in preeclampsia.[42-46] In addition, angiotensin AT-1 receptor antibody stimulates sFlt-1 secretion[47]. It is unclear if these alterations are pathogenic or epiphenomena.

**INCREASED SENSITIVITY TO ANGIOTENSIN II** — Increased sensitivity to angiotensin II has been described in preeclampsia,[48] and may be related to increased bradykinin (B2) receptor upregulation in preeclamptic patients. Upregulation leads to heterodimerization of B2 receptors with angiotensin II type I receptors (AT1), and this AT1/B2 heterodimer increases responsiveness to angiotensin II in vitro.[49]

As discussed above, patients with preeclampsia have increased levels of agonistic antibodies to the angiotensin AT-1 receptor. Angiotensin II is the endogenous ligand for the AT-1 receptor, thus increased activation of this receptor by auto-antibodies could induce the hypertension and vascular injury observed in preeclampsia. Studies in mice support this theory.[50]

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**GENETIC FACTORS** — Although most cases of preeclampsia are sporadic, genetic factors are thought to play a role in disease susceptibility.[51-60] A genetic predisposition to preeclampsia is suggested by the following observations:

- Primigravid women with a family history of preeclampsia (eg, affected mother or sister) have a two- to five-fold higher risk of the disease than primigravid women with no such history.[52,53,60,61]
- The risk of preeclampsia is increased more than seven-fold in women who have had preeclampsia in a previous pregnancy.[62]
- The spouses of men who were the product of a pregnancy complicated by preeclampsia are more likely to develop preeclampsia than spouses of men without this history.[53,59]
- A woman who becomes pregnant by a man whose previous partner had preeclampsia is at higher risk of developing the disorder than if the pregnancy with the previous partner was normotensive.[54]

These data suggest that both maternal and paternal contributions to fetal genes may have a role in defective placentation and subsequent preeclampsia. Several candidate genes, such as the angiotensinogen gene variant (T235), endothelial nitric oxide synthase (eNOS), and genes causing thrombophilia, have been linked with preeclampsia, but large studies have not shown them to be important for susceptibility to the disease.[50]

Genome wide scanning of 343 Icelandic women with preeclampsia, eclampsia, and gestational hypertension revealed a significant locus at 2p13.[55] Other susceptibility loci have been identified at 2p12, 2p25, and 9p13.[52,62,63] The genes for sFlt-1(Soluble

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fms–like tyrosine kinase 1) and Flt-1 are carried on chromosome 13. Fetuses with an extra copy of this chromosome (eg, trisomy 13) should produce more of these gene products than their normal counterparts. In fact, the incidence of preeclampsia in mothers who carry fetuses with trisomy 13 is greatly increased compared to all other trisomies or to control pregnant patients.[64] In addition, the ratio of circulating sFlt-1 to PlGF(placental growth factor) is significantly increased in these women, thus accounting for their increased risk of preeclampsia.[65]

A different locus at 12q may be linked to HELLP syndrome, but not preeclampsia without HELLP syndrome, suggesting that genetic factors important in HELLP syndrome tests, may be distinct from those in preeclampsia.[57]

**RISK FACTORS** — Risk factors for preeclampsia can be divided into 4 main catorgories.

**General factors**

- Age
- Obesity

**Genetic factors**

- Mother or sister with a history of preeclampsia

**Obstetric factors**

- Primiparity
- Multiple pregnancy

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- Previous preeclampsia
- Long birth interval
- Hydrops with a large placenta
- Hydatidiform mole
- Triploidy
- Trisomy 13

**Medical factors**

- Pre-existing hypertension
- Chronic kidney disease
- Diabetes (pre-existing and gestational)
- Antiphospholipid antibodies
- Connective tissue disease

The magnitude of risk depends upon the specific factor and is described below for selected risk factors evaluated in a systematic review of controlled studies.[66]

- A past history of preeclampsia increases the risk of developing preeclampsia in a subsequent pregnancy seven-fold compared to women without this history (RR 7.19, 95% CI 5.85-8.83).[66]

  The severity of preeclampsia strongly impacts this risk. Women with severe

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second trimester preeclampsia are at greatest risk of developing preeclampsia in a subsequent pregnancy: rates of 25 to 65 percent have been reported.[67-70] By comparison, women with mild preeclampsia in their first pregnancy develop preeclampsia in 5 to 7 percent of second pregnancies.[71,72] Women who had a normotensive first delivery develop preeclampsia in less than 1 percent of second pregnancies.

- First pregnancy (nulliparity) (RR 2.91, 95% CI 1.28-6.61).[66] It is unclear why the primigravid state is a significant predisposing factor. One theory is that these women may have had limited recent exposure to paternal antigens, which may play a role in the pathogenesis of the disease.
- A family history of preeclampsia in a first degree relative (RR 2.90, 95% CI 1.70-4.93)[66], suggesting a heritable mechanism in some cases.[73,74] The father of the baby may contribute to the increased risk, as the paternal contribution to fetal genes may have a role in defective placentation and subsequent preeclampsia.
- Preexisting medical conditions:
- Pregestational diabetes (RR 3.56, 95% CI 2.54-4.99), an effect that is probably related to a variety of factors, such as underlying renal or vascular disease, high plasma insulin levels/insulin resistance, and abnormal lipid metabolism.[75]

- Blood pressure ≥130/80 mm Hg at the first prenatal visit (RR 1.38-2.37)[66]. The risk of superimposed preeclampsia is highest in women with diastolic blood pressure ≥110 mm Hg (RR 5.2) and ≥100 mm Hg (RR 3.2) before 20 weeks of gestation.
- Antiphospholipid antibodies (RR 9.72, 95% CI 4.34-21.75).[66]
- Body mass index ≥ 26.1 kg/m$^2$ (RR 2.47, 95% CI 1.66-3.67).[66]

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- Twin pregnancies (RR 2.93, 95% 2.04-4.21).[66] The risk increases with increasing number of fetuses in multiple gestations: triplet pregnancy triples the risk of preeclampsia compared with twin pregnancy.
- Advanced maternal age (maternal age ≥40 RR 1.96, 95% CI 1.34-2.87 for multiparas and RR 1.68, 95% CI 1.23-2.29 for primiparas). Older women tend to have additional risk factors, such as diabetes mellitus and chronic hypertension. Whether adolescents are at higher risk of preeclampsia is more controversial[76]; a systematic review did not find an association.[66]

**Of note**, women who smoke cigarettes have a **lower** risk of preeclampsia than nonsmokers.

Additionally, some researchers have investigated the possibility of a seasonal relationship with the incidence of preeclampsia.[77-81] A difference in incidences of preeclampsia, examined exclusively on the basis of timing of delivery, have also been noted to have seasonal variation, but results have been inconsistent. This is not surprising, given that the studies were conducted in dissimilar populations, regions of the world, and climates, where environmental exposures may fluctuate greatly. Moreover, even if environmental factors are fairly constant across studies, the same exposure may have a vastly different impact on the pathophysiologic condition of preeclampsia in distinct populations of pregnant women, depending on their underlying characteristics.

In Kuwait, it was found that the incidence of pregnancy-induced hypertension per 1,000 deliveries was high in June when the temperature was very high and the

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humidity at its lowest. Interestingly, the reverse was true for preeclampsia. The incidence of preeclampsia was highest in November when the temperature was low and the humidity high.[78]

In Norway, a country with substantial differences in climate in summer and winter, Magnus et al aimed to demonstrate a seasonal pattern in the incidence of preeclampsia. Among all 1,869,388 births from 1967–1998 in

Norway, 51,801 (2.77%) were recorded with preeclampsia. The incidence of preeclampsia was found to be highest (3.08%) in December. The incidence declined during spring and summer to the lowest level (2.46%) in August and then increased again gradually in the autumn months. The prevalence ratio for preeclampsia was 1.25 for December, with August as the reference month. Adjustment for other variables did not alter the seasonal trend in occurrence of preeclampsia.

In Zimbabwe, a study by Wacker et al supported the concept of a seasonal change for preeclampsia. At the start of the rainy season there was a peak incidence of preeclampsia. On the other hand a lower incidence of preeclampsia can be found in months with a very low or even no rainfall. It is questionable whether this phenomenon is explained by a direct connection between humidity and temperature on blood pressure or by an indirect effect of the climate via other factors.

In a recent publication it was reported that preeclampsia occurred more often at Tygerberg Hospital[82] during the winter months. (13.6% of admissions in winter vs. 11.5% of all annual admissions). Women admitted in winter had a higher risk of

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developing preeclampsia compared to those admitted in summer (OR_1.69, 95% CI: 1.07_1.53). The risk of developing preeclampsia in June was significantly higher than in February (OR_2.81, 95% CI: 2.06_ 3.83). However, one shortcoming of that study was the unavailability of gestational age at the time of delivery. This may be important, as underlying factors which may play a role in the development of preeclampsia may do so nearer to the time of conception rather than at the time of clinical recognition of disease.[83]

It is unclear why a seasonal variation in preeclampsia is found. Other studies have also shown seasonal variation in diseases, such as cardiovascular events.[89,90] Winter peaks have been reported for myocardial infarction, fatal pulmonary thrombo-embolism, deep venous thrombosis and non-traumatic rupture of the thoracic aorta. This evidence suggests that diseases might be influenced by weather conditions.

Some hypotheses have been presented to explain the variation specifically in preeclampsia. There is growing evidence of increased enhanced maternal intravascular systemic inflammatory response in patients with preeclampsia.[1] Maternal infections may enhance this response. Seasonal fluctuations in infections may lead to variability in the seasonal occurrence of preeclampsia.[84] Seasonal variation in preeclampsia has also been linked to diet.[80]

In humans, plasma volume demonstrates seasonal variation. Plasma volume contracts during the winter months and expands in the warm summer months.[85] There is evidence that pre-conceptual factors influencing plasma volume may be central to the

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development of preeclampsia. This may contribute to the seasonal variation previously referred to. It is plausible that the incidence of preeclampsia would be highest if conception occurred shortly after the prolonged plasma volume constriction of winter. This would account for a potentially accelerated volume expansion in early pregnancy (during the summer) superimposed on a volume-restricted condition.[86]

In our study, we aim to analyze the incidence of preeclampsia by both the timing of delivery AND the timing of conception. As Tygerberg hospital is a referral center and a tertiary level hospital, this study could provide valuable information in predicting and managing an increased patient load. It will also allow us to improve counselling of high risk patients and facilitate in planning their future pregnancies.

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# Materials and methods

We performed a retrospective descriptive study of all women with preeclampsia who delivered at Tygerberg Hospital in 2010. Names of patients were identified from labour ward records. In addition, the records of all women from the department where a platelet count as well as a haemoglobin value were done in 2010 were traced and examined to determine whether she had preeclampsia.

Preeclampsia was diagnosed as hypertension associated with proteinuria after the 20th week of gestation.[84] Hypertension was defined as a blood pressure of at least140 / 90 mm Hg on at least two occasions 4–6 h apart. Proteinuria was defined as the excretion of 300 mg or more of protein in a 24 h period or as a protein>1 + on dipstick in at least two random urine samples taken at least 4–6 h apart.

Once the folder was located, data was collected and recorded on a data-sheet. Apart from demographic data, previous pregnancy outcomes as well as previous medical and surgical history were documented.

Duration of pregnancy was considered to be accurate if the date of last menstruation was known and corresponded to the clinical examination or an ultrasound performed before 24 weeks′ gestation, or alternatively if an early ultrasound was available without the patient being certain of her last menstruation. Duration of pregnancy

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based on SF-measurement or a late ultrasound was considered to be uncertain. Laboratory investigations were documented and considered to be abnormal based on local laboratory recommendations. All antihypertensive drugs used, as well as the use of MgSO4 and heparin, were recorded. Initial management was divided into stabilisation and delivery, where the intention was to deliver the patient not longer than 48 hours after admission, or expectant, where the managing physician planned to postpone delivery for more than 48 hours. Vaginal delivery was divided into following spontaneous onset or induction of labour. Methods of induction of labour could include misoprostol, prepidil®, oxytocin or artificial rupture of membranes. Indications for caesarean section were divided into the following groups: fetal distress (including abruptio placentae), failed induction of labour, maternal condition or other. The last umbilical artery Doppler test was recorded and was reported as below the 75$^{th}$ centile (p75), between p75 and p95, above p95, absent enddiastolic velocity and reversed end diastolic velocity.[87]

Complications were defined as follows:

- Eclampsia: Eclampsia is defined as the onset of convulsions in a woman with preeclampsia.
- HELLP syndrome: The diagnosis is established by the following criteria:
    - Microangiopathic hemolytic anemia with characteristic schistocytes on blood smear
    - Platelet count <100,000 cells/µL
    - Serum lactate dehydrogenase >600 IU/L or total bilirubin >1.2 mg/dL
    - Serum aspartate aminotransferase (AST) >70 IU/L

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- Pulmonary edema: Clinically diagnosed, confirmed by chest X-ray
- Intracranial haemorrhage: Diagnosed by computerised tomography
- Liver failure: Clinically diagnosed in a patient with jaundice and encephalopathy, confirmed by raised transaminases
- Renal injury or insult: Serum creatinine doubles
- Renal failure: Serum creatinine increases 3-fold
- Ascites: Clinically diagnosed ascites confirmed by ultrasound
- Placental insufficiency / Intrauterine growth restriction (IUGR): Estimated fetal weight below the 10 centile for gestational age with abnormal umbilical artery dopplers
- Abruptio placentae: the typical clinical picture (bleeding after 20 weeks gestational age, an irritable or hypertonic uterus and a tender uterus or abdominal pain) or a retroplacental clot causing an indentation covering 15% or more of the maternal surface of the placenta or histological proven abruptio placentae.

Data were primarily analysed in relation to the season of delivery and also the preconception season. Summer was diagnosed as lasting from summer solstice (21 December) to autumn equinox (20 March), autumn as lasting from autumn equinoxtill winter solstice (21 June), winter as lasting from winter solstice till spring equinox (23 September) and spring as lasting from spring equinox till summer solstice.[88]

The date of the last normal menstruation was accepted in the cases where patients were certain of their dates if the dates corellated with clinical findings. When any other way was used to calculate the gestational age, the date of the last normal menstruation was extrapolated as day 0 in relation to the calculated gestational age in days. The same analyses in relation to the season of delivery and the season of the

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last menstruation were repeated for both all patients and only patients where the date of the last normal menstruation was certain.

The data was analyzed using the SPSS software (Statistical Package for Social Science). Discrete data was compared by calculating relative risks with 95% confidence limits, as well as the $chi^2$ test. Fisher's exact test was used to compare ratios where the expected value in any cell of a two-by-two table is less than five. The means of normally distributed continuous data was compared by analysis of variance, while the medians of continuous data which are not distributed normally, where calculated using the non-parametric Mann Whitney u test. A p-value of $< 0.05$ was considered to be statistically significant, where applicable.

The study protocol was approved by the Committee for Human Research, of the University of Stellenbosch (Project Number: N11/06/190).

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# Results

## Analyses based on season of delivery

We admitted 984 patients with preeclampsia during 2010. Of these women, 169 delivered in summer, 264 in the autumn, 317 in winter and 234 in spring. (Table 1). There were no differences in the demographics of mothers who delivered in the various seasons, but the gestational age at delivery was significantly higher in summer than in spring.

| | **Summer** | **Autumn** | **Winter** | **Spring** | **All** | **p-value** |
|---|---|---|---|---|---|---|
| Age (years) | 25.8 ± 6.14 | 26 ± 6.06 | 26 ± 6.62 | 24.9 ± 6.53 | 25.5 ± 6.3 | 0.161 |
| Gravidity | 1 (1 – 8) | 2 (1 – 7) | 1 (1 – 9) | 2 (1 – 7) | 2 (1 – 9) | 0.389 |
| Parity | 0 (0 – 5) | 0 (0 – 5) | 0 (0 – 8) | 0 (0 – 5) | 0 (0 – 8) | 0.717 |
| Maternal weight (kg) | 70.7 ± 17.6 | 73.9 ± 18.1 | 73.0 ± 17.5 | 71.8 ± 20.6 | 72.2 ± 18.7 | 0.303 |
| Maternal Height (cm) | 157.6 ± 7.1 | 158.1 ± 6.1 | 157.4 ± 7.1 | 158.2 ± 6.4 | 157.9 ± 6.6 | 0.590 |
| BMI (kg/m$^2$) | 28.4 ± 6.6 | 29.6 ± 6.6 | 29.6 ± 6.9 | 28.5 ± 7.9 | 29.0 ± 7.1 | 0.169 |
| Gestational age (days) | 252.4 ± 29.0 | 248.0 ± 28.7 | 249.0 ± 29.9 | 243.5 ± 31.2 | 248.0 ± 29.9 | 0.025 |

Table 1: Some demographic data of women according to the season of birth.

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There was a significant difference in the number of women admitted with preeclampsia in each of the four seasons compared with the other three (Table 2, $p < 0.001$), as well as between those who delivered in the different months of the year. (Table 3, $p < 0.001$ ). There was a similar significant difference when the distribution of admissions of preeclampsia below 34 weeks' gestation was considered.

| | **Summer** | **Autumn** | **Winter** | **Spring** | **All patients** |
|---|---|---|---|---|---|
| Total Births | 1489 | 1541 | 1669 | 1595 | 6294 |
| Preeclampsia cases | 169 | 264 | 317 | 234 | 984 |
| % of deliveries with preeclampsia | 11.35 | 17.14 | 18.99 | 14.67 | 15.63 |
| Preeclampsia cases < 34 weeks' gestation | 49 | 98 | 102 | 91 | 340 |
| % of deliveries with preeclampsia < 34 weeks' gestation | 3.29 | 6.36 | 6.11 | 5.71 | 5.40 |

Table 2: The incidence of preeclampsia according to season of birth.

| Month | Cases | Total births during month | Cases as % of total births | % of annual cases |
|---|---|---|---|---|
| January | 89 | 508 | 17.5 | 9.0 |
| February | 38 | 460 | 8.3 | 3.9 |
| March | 37 | 503 | 7.4 | 3.8 |
| April | 99 | 527 | 18.8 | 10.1 |
| May | 92 | 514 | 17.9 | 9.3 |
| June | 83 | 506 | 16.4 | 8.4 |
| July | 104 | 584 | 17.8 | 10.6 |
| August | 101 | 568 | 17.8 | 10.3 |
| September | 113 | 523 | 21.6 | 11.5 |
| October | 85 | 534 | 15.9 | 8.6 |
| November | 76 | 559 | 13.6 | 7.7 |
| December | 67 | 508 | 13.2 | 6.8 |

Table 3: The incidence of preeclampsia according to month of birth.

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The gestational age at delivery remained significantly different if only mothers where the last normal menstruation was certain were considered. (Figure 1).

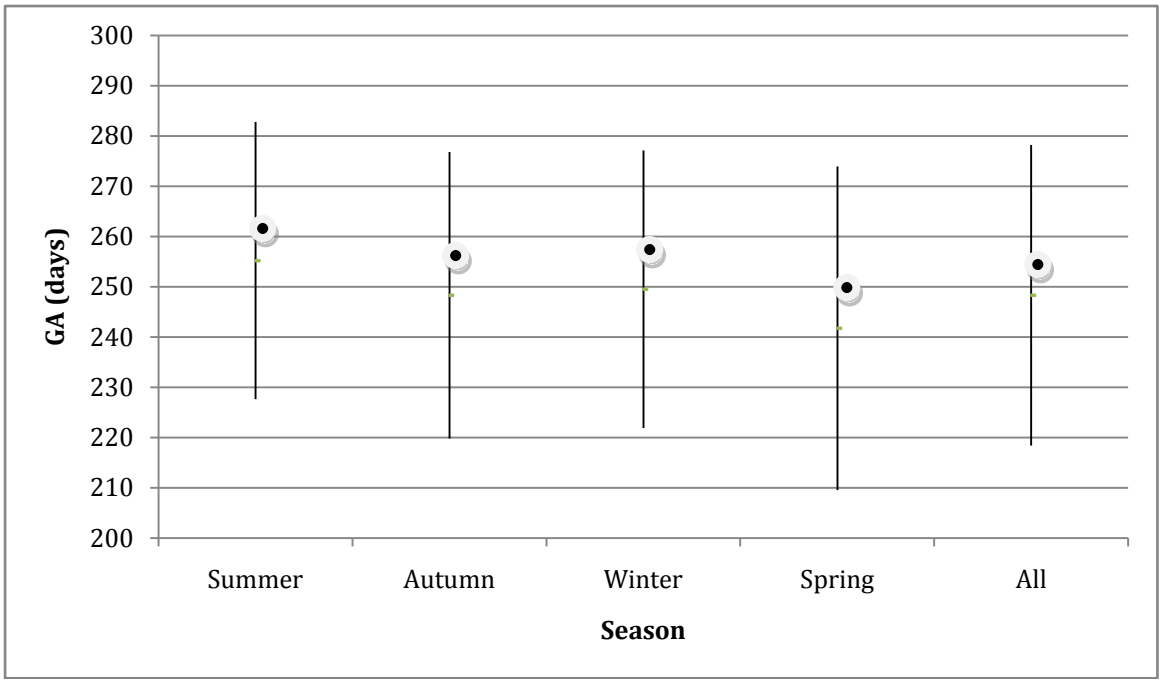


Figure 1: The mean and standard deviation of the gestational age at birth in days, according to season of birth.

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Fifty-eight women presented before 28 weeks' gestation. (Table 4, p = 0.005). The same data is presented as percentages in figure 2.

| | **Summer** | **Autumn** | **Winter** | **Spring** | **All** |
|---|---|---|---|---|---|
| <24 Weeks(w) | 0 | 0 | 1 | 2 | 3 |
| 24w – 27w6days(d) | 6 | 9 | 21 | 19 | 55 |
| 28w – 33w6d | 43 | 89 | 80 | 70 | 282 |
| 34w – 37w6d | 49 | 76 | 96 | 69 | 290 |
| ≥38w | 71 | 90 | 119 | 74 | 354 |
| TOTAL | 169 | 264 | 317 | 234 | 984 |

Table 4: The distribution of gestational age at birth in categories depending on the season of birth.

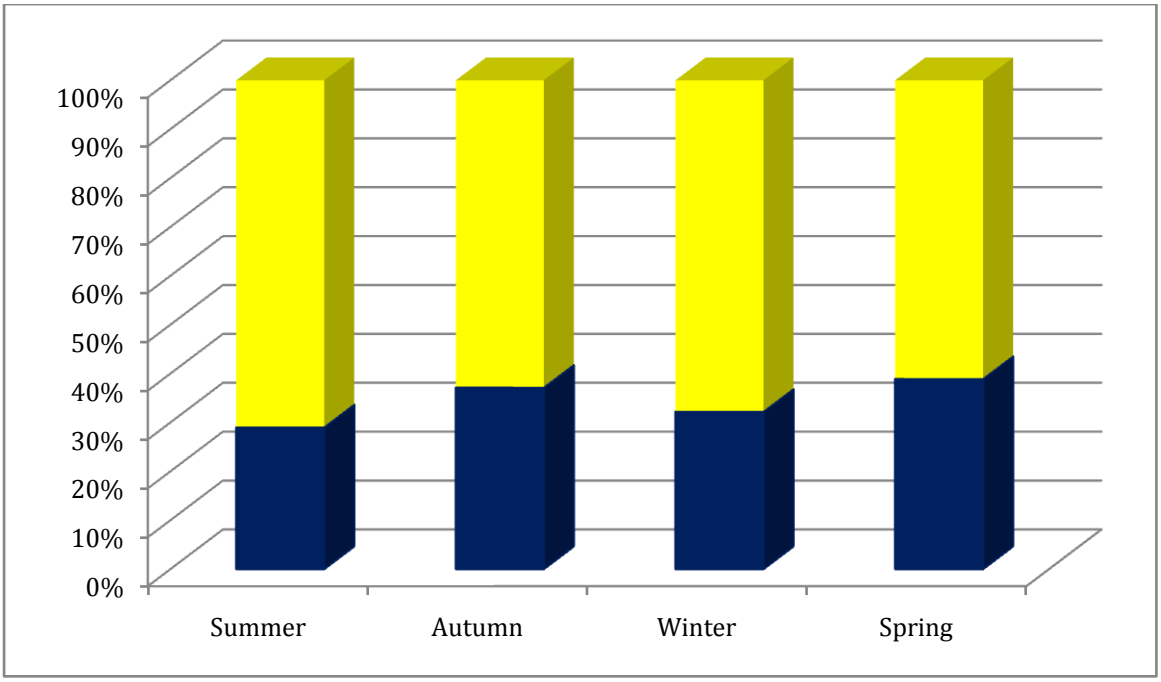


Figure 2: The distribution of gestational age as percentages above and below 34 weeks' gestation in the different seasons of birth.

The gestational age could be determined accurately in two-thirds of all women. (Table 5). The level of accurate dates did not differ between seasons. The method used to calculate the gestational age could not be determined in 9 cases.

| | **Summer** | **Autumn** | **Winter** | **Spring** | **Total** |
|---|---|---|---|---|---|
| Gestational age sure | 105 (63.6%) | 178 (68.2) | 220 (69.8%) | 148 (63.2%) | 651 (66.8%) |
| Gestational age unsure | 60 (36.4%) | 83 (31.8%) | 95 (30.2%) | 86 (36.8%) | 324 (33.2%) |

Table 5: The degree of certainty of gestational age in the different seasons.

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While expectant management was attempted in 11.5% of all cases, management did not differ during the different seasons of delivery. (Table 6).

| | **Summer** | **Autumn** | **Winter** | **Spring** | **TOTAL** |
|---|---|---|---|---|---|
| Expectant management | 21 | 29 | 30 | 33 | 113 |
| Stabilise and deliver | 148 | 235 | 287 | 201 | 871 |
| | 169 | 264 | 317 | 234 | 984 |

Table 6: The distribution of attempts to expectant management according to season of birth.

This was also true when analysis was limited to only cases which would have normally been considered for expectant management, namely those who presented between 24 weeks' gestation but before 34 weeks' gestation. (Table 7).

| | Summer | Autumn | Winter | Spring | TOTAL |
|---|---|---|---|---|---|
| Expectant management | 15 | 23 | 25 | 23 | 86 |
| Stabilise and deliver | 34 | 75 | 76 | 66 | 251 |
| | 49 | 98 | 101 | 89 | 337 |

Table 7: The distribution of attempts to expectant management according to season of birth in patients who would normally be considered for expectant management.

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There was no difference in days gained with expectant management in women delivering in the different seasons. (Table 8).

| | **Median (minimum – maximum)** |
|---|---|
| Summer | 8 (1 – 24) |
| Autumn | 10 (3 – 28) |
| Winter | 8 (3 – 19) |
| Spring | 10 (1 – 30) |

Table 8: The median number of days gained with expectant management according to the season of delivery.

Induction of labour was attempted in 248 cases. There was no difference in the number of cases in each season where induction of labour was attempted. (Table 9, p = 0.11). The methods used to induce labour differed significantly depending on the season birth. (Table 10, p = 0.001).

| | **Summer** | **Autumn** | **Winter** | **Spring** |
|---|---|---|---|---|
| Cases where induction of labour was attempted | 45 | 56 | 93 | 54 |
| Percentage of all pre-eclamptics where induction of labour was attempted | 26.6 | 21.2 | 29.3 | 23.1 |

Table 9: The number of cases where induction of labour was attempted based on the season of delivery.

| | Summer | Autumn | Winter | Spring |
|---|---|---|---|---|
| Misoprostol | 17 | 20 | 44 | 23 |
| ROM / Oxytocin | 3 | 24 | 48 | 18 |
| Prepidil | 24 | 12 | 20 | 13 |

Table 10: The methods used for induction of labour according to season of delivery.

The caesarean section incidence was 59.8%. This did not depend on the season of delivery. (Table 11, p = 0.33). The indication for caesarean section did not depend on the season of delivery. (Table 11. p= 0.56).

| | Summer (n = 169) | Autumn (n = 264) | Winter (n = 317) | Spring (n = 234) |
|---|---|---|---|---|
| Caesarean sections | 94 | 170 | 178 | 146 |
| • Fetal Distress | 41 | 103 | 98 | 96 |
| • Failed induction of labour | 19 | 23 | 29 | 21 |
| • Maternal | 11 | 9 | 12 | 5 |
| • Other | 22 | 35 | 39 | 23 |

Table 11: The indications for caesarean section according to season of delivery.

The mean creatinine values were significantly higher in autumn than in spring (Table 12, $p < 0.001$), but none of the other biochemical tests differed between the seasons.

| | Urea mmol/l | Creatinine mcmol/l | Haemoglobin g/dl | Platelets x10^9 | AST U/l | LDH U/l | 24hr urinary protein g/24hr | Creatinine Clearance ml/min |
|---|---|---|---|---|---|---|---|---|
| Summer | 3.93 ± 1.96 | 77.93 ± 27.93 | 11.33 ± 1.65 | 224 (25 – 437) | 109.32 ± 171.94 | 643.26 ± 557.65 | 2.47 ± 3.12 | 100.70 ± 37.48 |
| Autumn | 4.17 ± 3.43 | 83.91 ± 75.41 | 11.51 ± 1.99 | 212.5 (42 – 516) | 172.09 ± 564.88 | 756.56 ± 1463.71 | 2.44 ± 3.33 | 111.86 ± 34.86 |
| Winter | 3.86 ± 2.80 | 77.61 ± 44.60 | 11.65 ± 5.26 | 230 (22 – 626) | 210.03 ± 329.17 | 755.35 ± 632.08 | 2.435 ± 3.42 | 123.21 ± 77.65 |
| Spring | 4.06 ± 2.40 | 64.46 ± 40.64 | 13.73 ± 2.50 | 203.5 (31 – 697) | 157.00 ± 242.40 | 656.37 ± 436.42 | 3.05 ± 3.32 | 82.68 ± 20.52 |
| Total | 4.00 ± 2.78 | 76.21 ± 52.26 | 12.05 ± 12.63 | 217 (22 – 697) | 164.23 ± 367.90 | 713.76 ± 914.07 | 2.62 ± 3.29 | 100.22 ± 44.17 |

Table 12: The results of laboratory investigations (mean ± standard deviation) in the various seasons of birth.

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There was a statistically significant difference in the number of women receiving different medications in the different seasons of birth. (Table 13).

| | Summer | Autumn | Winter | Spring | All | p-value |
|---|---|---|---|---|---|---|
| Methyldopa | 58.0 | 64.0 | 44.8 | 51.3 | 53.8 | 0.0001 |
| Nifedipine | 68.0 | 90.2 | 97.2 | 97.9 | 90.4 | 0.0001 |
| Nifedipine XL | 51.5 | 48.9 | 30.6 | 46.2 | 42.8 | 0.0001 |
| Labetalol | 14.8 | 10.6 | 18.9 | 23.1 | 17.0 | 0.002 |
| $MgSO_4$ | 30.2 | 29.2 | 24.6 | 41.5 | 30.8 | 0.0001 |
| Heparin | 18.3 | 14.8 | 11.0 | 9.0 | 12.8 | 0.023 |

Table 13: The percentage of women delivering in the various seasons of the year who required different medications.

Two hundred and fifteen women underwent a Doppler assessment of the umbilical artery. Fifty-two women (5.3%) had either absent end-diastolic flow (AEDF) or reversed end-diastolic flow (REDF). There were no statistically significant differences in the distribution of Doppler results in the different seasons.

| | Summer | Autumn | Winter | Spring | All |
|---|---|---|---|---|---|
| < 75$^{th}$ Centile | 7 | 22 | 19 | 9 | 57 |
| 75$^{th}$ – 95$^{th}$ centile | 10 | 20 | 22 | 16 | 68 |
| > 95$^{th}$ Centile | 6 | 17 | 6 | 9 | 38 |
| AEDF | 5 | 7 | 13 | 13 | 38 |
| REDF | 5 | 1 | 3 | 5 | 14 |

Table 14: The distribution of normal and abnormal umbilical artery Doppler tests during the various seasons.

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The occurrence of different complications in each of the seasons of delivery is depicted in Table 15. There were no statistically significant differences in any of the groups.

| | **Summer (n = 169)** | **Autumn (n = 264)** | **Winter (n = 317)** | **Spring (n = 234)** | **All (n = 984)** |
|---|---|---|---|---|---|
| Eclampsia | 15 | 27 | 23 | 17 | 82 |
| HELLP syndrome | 13 | 17 | 21 | 21 | 72 |
| Pulmonary embolus | 5 | 7 | 6 | 6 | 24 |
| Intracranial haemorrhage | 1 | 0 | 0 | 0 | 1 |
| Liver failure | 0 | 0 | 0 | 0 | 0 |
| Renal injury | 6 | 22 | 18 | 8 | 54 |
| Renal failure | 1 | 4 | 4 | 4 | 13 |
| Ascites | 9 | 6 | 13 | 10 | 38 |
| Placental insufficiency | 11 | 26 | 23 | 22 | 82 |
| Intrauterine death | 2 | 7 | 13 | 11 | 33 |
| Abruptio placentae | 5 | 10 | 14 | 13 | 42 |

Table 15: The occurrence of different complications in each of the seasons of delivery.

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Some determinants of the pregnancy outcome are shown in table 16. The neonatal and placental weights were significantly higher in summer. The same level of statistical significance was found when only liveborn babies were considered. (Placental data not shown for liveborns). There was no difference in five minute Apgar scores < 7 between the seasons of delivery.

| | **Neonatal weight(g) (all)** | **Neonatal weight(g) (liveborns)** | **Male babies** | **Placenta l weight(g ) (all)** | **Apgar 1 minute** | **Apgar 5 minutes** | **Apgar 10 minutes** |
|---|---|---|---|---|---|---|---|
| Summer (n = 169) | 2436.4 ± 929.6 | 2480.0 ± 907.6 | 88 | 547.3 ± 184.5 | 9 (0 – 10) | 10 (0 – 10) | 10 (0 – 10) |
| Autumn (n = 264) | 2229.6 ± 844.9 | 2254.1 ± 849.3 | 123 | 502.2 ±182.1 | 8 (0 – 10) | 9 (0 – 10) | 10 (0 – 10) |
| Winter (n = 317) | 2297.5 ± 886.7 | 2335.7 ± 872.2 | 150 | 526.0 ± 194.1 | 8 (0 – 10) | 9 (0 – 10) | 10 (0 – 10) |
| Spring (n = 234) | 2153.8 ± 951 | 2224.9 ± 939.3 | 108 | 485.0 ± 177.2 | 8 (0 – 10) | 9 (0 – 10) | 10 (0 – 10) |

Table 16: Pregnancy outcomes in relation to season of delivery.

More women who delivered in summer admitted to smoking. (Table 17, p = 0.047).

There was no difference in the reported incidence of alcohol or drug abuse.

| | **Summer (n = 169)** | **Autumn (n = 264)** | **Winter (n = 317)** | **Spring (n = 234)** |
|---|---|---|---|---|
| Smokers | 39 (23.1%) | 38 (14.4%) | 42 (13.2%) | 38 (16.2%) |
| Alcohol abusers | 25 | 22 | 27 | 20 |
| Drug abusers | 6 | 5 | 3 | 0 |

Table 17: Users of tobacco, alcohol and drugs according to season of delivery.

## Analyses based on season of assumed conception

Almost 30% of women with preeclampsia had their last menstrual period during the spring, while the smallest number of women last menstruated in winter. (Table18). The distribution of last menstrual period according to month is illustrated in table 19.

| SEASON | *n* | Percentage of pre-eclamptics |
|---|---|---|
| Summer | 245 | 24.9 |
| Autumn | 229 | 23.3 |
| Winter | 218 | 22.2 |
| Spring | 292 | 29.7 |

Table: 18 The occurrence of preeclampsia according to the season during which the last normal menstruation took place.

| MONTH | *n* | Percentage of pre-eclamptics |
|---|---|---|

| | | |
|---|---|---|
| January | 89 | 9.0 |
| February | 74 | 7.5 |
| March | 80 | 8.1 |
| April | 97 | 9.9 |
| May | 58 | 5.9 |
| June | 65 | 6.6 |
| July | 55 | 5.6 |
| August | 80 | 8.1 |
| September | 94 | 9.6 |
| October | 87 | 8.8 |
| November | 111 | 11.3 |
| December | 94 | 9.6 |

Table: 19 The occurrence of preeclampsia according to the month during which the last normal menstruation took place.

There were no differences in the demographics of mothers who had their last normal menstruation in the various seasons, but the gestational age at delivery was significantly higher in women who menstruated in winter than in summer. This difference remained when only women with certain gestational age were considered. The gestational age at delivery of women with certain gestational age who last menstruated in winter was 254.9 ± 25.9 days compared with 240.7 ± 31.2 days in the group who menstruated in summer. ($p = 0.0004$).

| | Summer | Autumn | Winter | Spring | All | p-value |
|---|---|---|---|---|---|---|
| Age | 25.44 ± 6.33 | 25.90 ± 1.23 | 25.22 ± 5.80 | 25.33 ± 6.67 | 25.46 ± 6.34 | 0.67 |
| Gravidity | 2 (1 – 7) | 2 (1 – 7) | 1 (1 – 8) | 2 (1 – 9) | 2 (1 – 9) | 0.79 |
| Parity | 0 (0 – 5) | 0 (0 – 5) | 0 (0 – 5) | 0 (0 – 8) | 0 (0 – 8) | 0.44 |
| Maternal weight | 72.84 ± 18.05 | 73.80 ± 18.24 | 70.67 ± 17.50 | 71.56 ± 20.36 | 72.23 ± 18.70 | 0.35 |
| Maternal Height | 158.30 ± 5.88 | 157.73 ± 6.80 | 156.82 ± 7.41 | 158.44 ± 6.48 | 157.89 ± 6.64 | 0.182 |
| BMI | 29.02 ± 6.63 | 34.95 ± 4.67 | 28.77 ± 6.97 | 28.33 ± 7.77 | 28.96 ± 7.11 | 0.182 |
| Gestation at birth | 242.96 ± 30.38 | 244.55 ± 32.67 | 253.56 ± 27.36 | 250.90 ± 27.92 | 248.03 ± 29.85 | 0.000 |

Table 20: Some demographic detail of women with preeclampsia depending on the season of their last menstruation.

The laboratory test results of women were not influenced by the season of their last normal menstruation. (Table 21).

| Season of LMP | Urea mmol/l | Creatinine Mcmol/l | Hemoglobin g/dl | Platelets X 10^9 | AST U/l | LDH u/l |
|---|---|---|---|---|---|---|

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Autumn | N | 226 | 228 | | 229 | 34 | 28 |
| | Mean ± S Dev | 4.1 ± 2.2 | 73.0 ± 30.3 | | 219.0 ± 92.4 | 130.1 ± 196.4 | 680.3 ± 605.1 |
| Spring | N | 282 | 292 | | 292 | 39 | 42 |
| | Mean ± S Dev | 4.0 ± 2.5 | 77.5 ± 29.3 | | 226.9 ± 93.9 | 188.1 ± 542.7 | 723.8 ± 1318.9 |
| Summer | N | 237 | 245 | 245 | 245 | 23 | 21 |
| | Mean ± S Dev | 3.9 ± 2.8 | 69.5 ± 51.9 | | 223.8 ± 100.0 | 296.2 ± 388.3 | 1057.2 ± 727.2 |
| Winter | N | 215 | 216 | 218 | 216 | 28 | 26 |
| | Mean ± S Dev | 4.0 ± 3.6 | 85.4 ± 84.3 | | 216.2 ± 83.5 | 64.1 ± 67.1 | 456.2 ± 190.3 |
| Total | N | 960 | 981 | 984 | 982 | 124 | 117 |
| | Mean ± S Dev | 4.0 ± 2.8 | 76.2 ± 52.3 | | 221.9 ± 92.9 | 164.2 ± 367.9 | 713.8 ± 914.0 |

Table 21: The distribution of laboratory results depending on the season of last menstruation.

The medication required differed significantly when analysis was performed in the different groups based on their last menstrual periods. (Figure 3).

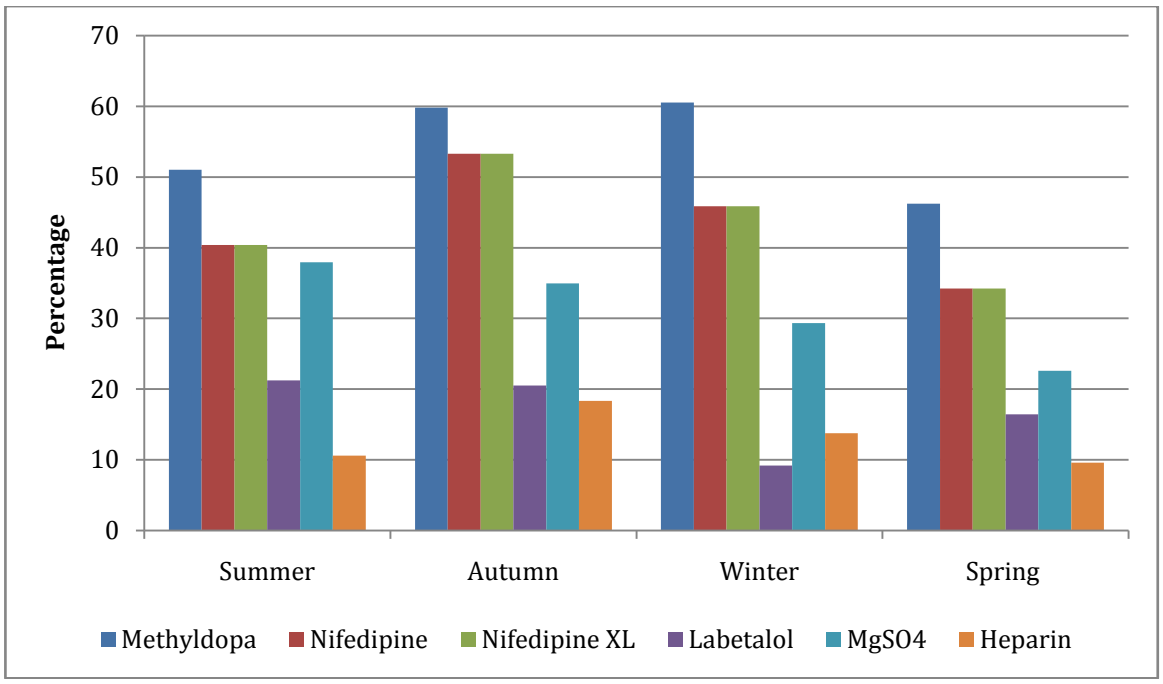


Figure 3: The percentage of women receiving different medications based on the season of their last menstruation.

There were 337 cases where the gestational age was more than 168 days (24 weeks) but less than 238 days (34 weeks). Expectant management was attempted in 113 cases. Expectant management was attempted significantly more often in women who had last menstruated in autumn. (Table 22, p = 0.048).

| Immediate Management | Summer | Autumn | Winter | Spring |
|---|---|---|---|---|
| Expectant | 26 | 38 | 20 | 29 |
| Stabilize and delivered | 219 | 191 | 198 | 263 |

Table 22: the initial approach to management of women with preeclampsia according to the season of their last menstruation.

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Significantly more days were gained with expectant management in women who had last menstruated in autumn. (Table 23).

| | **Median (minimum – maximum)** |
|---|---|
| Summer | 7.5 (2 – 19) |
| Autumn | 12.5 (1 – 30) |
| Winter | 8 (1 – 28) |
| Spring | 8 (3 – 19) |

Table 23: The median number of days gained with expectant management according to the last menstruation of the woman.

Induction of labour was attempted in 248 cases. There was no difference in the number of cases in each season where induction of labour was attempted. (Table 24, p = 0.19). However, the primary methods used to induce labour differed significantly depending on the season of the last normal menstruation. (Table 25, p = 0.002).

| | **Summer** | **Autumn** | **Winter** | **Spring** |
|---|---|---|---|---|
| Cases where induction of labour was attempted | 58 | 54 | 49 | 87 |
| Percentage of all preeclamptics where induction of labour was attempted | 23.7 | 23.6 | 22.5 | 29.8 |

Table 24: The number of cases where induction of labour was attempted based on the last normal menstruation.

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| | Summer | Autumn | Winter | Spring |
|---|---|---|---|---|
| Misoprostol | 26 | 17 | 18 | 43 |
| ROM / Oxytocin | 21 | 9 | 18 | 25 |
| Prepidil | 10 | 27 | 13 | 19 |
| Unknown | 1 | 1 | 0 | 0 |

Table 25: The methods used for induction of labour according to last normal menstruation.

The caesarean section incidence was 59.8%. This did not depend on the season of last menstruation. (Table 26, p = 0.33). The indication for caesarean section did not differ between the seasons of last menstruation. (Table 26. P = 0.56).

| | Summer (n = 245) | Autumn (n = 229) | Winter (n = 218) | Spring (n = 292) |
|---|---|---|---|---|
| Caesarean sections | 153 | 144 | 127 | 164 |
| • Fetal Distress | 91 | 79 | 73 | 95 |
| • Failed induction of labour | 28 | 24 | 19 | 20 |
| • Maternal | 11 | 9 | 8 | 9 |
| • Other | 23 | 30 | 27 | 40 |

Table 26: The indications for caesarean section according to last normal menstruation.

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There was no difference in the degree of abnormality found in the 215 women who had undergone an umbilical artery Doppler assessment prior to delivery. (Table 27, p = 0.14)

| | Summer | Autumn | Winter | Spring | Total |
|---|---|---|---|---|---|
| Below 75th Centile | 12 | 10 | 15 | 20 | 57 |
| 75th to 94th centile | 23 | 16 | 14 | 15 | 68 |
| 95th centile and above | 6 | 12 | 6 | 14 | 38 |
| Absent enddiastolic flow velocity | 6 | 17 | 7 | 8 | 38 |
| Reversed enddiastolic flow velocity | 4 | 4 | 3 | 3 | 14 |
| TOTAL | 51 | 59 | 45 | 60 | 215 |

Table 27: Umbilical artery Doppler results according to last normal menstruation.

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The season of last normal menstruation did not influence the incidence of complications as depicted in table 28.

| COMPLICATION | Summer N = 245 | Autumn N = 229 | Winter N = 218 | Spring N = 292 | p-value |
|---|---|---|---|---|---|
| Eclampsia | 18 | 24 | 21 | 19 | 0.33 |
| HELLP syndrome | 21 | 19 | 13 | 19 | 0.62 |
| Pulmonary edema | 9 | 6 | 4 | 5 | 0.40 |
| Intracranial haemorrhage | 0 | 0 | 1 | 0 | 0.32 |
| Liver failure | 0 | 0 | 0 | 0 | * |
| Renal injury/insult | 16 | 7 | 13 | 18 | 0.06 |
| Renal failure | 3 | 3 | 2 | 5 | 0.89 |
| Ascites | 7 | 12 | 8 | 11 | 0.60 |
| Pl ins/IUGR | 21 | 22 | 16 | 23 | 0.83 |
| Intrauterine death | 12 | 5 | 4 | 12 | 0.18 |
| Abruptio placentae | 14 | 9 | 10 | 9 | 0.50 |

Table 28: The occurrence of complications according to the season of the last normal menstruation.

Some determinants of the pregnancy outcome are summarized in table 29. The neonatal and placental weights were significantly higher in women whose last normal menstruation was in spring or winter. The same level of statistical significance was found when only liveborn babies were considered. (Placental data not shown for liveborns).

| | **Neonatal weight(g) (all)** | **Neonatal weight(g) (liveborns)** | **Male babies** | **Placental weight(g) (all)** | **Apgar 1 minute** | **Apgar 5 minutes** | **Apgar 10 minutes** |
|---|---|---|---|---|---|---|---|
| Autumn | 2203.9 ± 990.73 | 2291.2 ± 966.8 | 116 (50.7%) | 509.46 ± 191.9 | 9.00 (0-10) | 9.00 (0-10) | 10.00 (0 – 10) |
| Spring | 2335.15 ± 873.2 | 2371.35 ± 860.9 | 134 (45.9%) | 534.76 ± 198.7 | 9.00 (0-10) | 9.00 (0-10) | 10.00 (0 – 10) |
| Summer | 2151.20 ± 906.8 | 2182.43 ± 908.0 | 111(45.3%) | 480.4 ± 177.1 | 8.00 (0 – 10) | 9.00 (0-10) | 10.00 (0 – 10) |
| Winter | 2382.63 ± 820.6 | 2404.00 ± 818.5 | 108 (49.5%) | 527.31 ± 168.8 | 8.00 (0 – 10) | 9.00 (0-10) | 10.00 (0 – 10) |

Table 29: Pregnancy outcomes in relation to season of last normal menstruation.

More women who menstruated in summer admitted to smoking. (Table 30, p = 0.047). There was no difference in the reported incidence of alcohol or drug abuse.

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| | **Summer (n = 245)** | **Autumn (n = 229)** | **Winter (n = 218)** | **Spring (n = 292)** |
|---|---|---|---|---|
| Smokers | 42 (20.5%) | 47 (15.1%) | 24 (17.1%) | 44 (11.0%) |
| Alcohol abusers | 27 | 23 | 22 | 22 |
| Drug abusers | 0 | 5 | 5 | 4 |

Table 30: Users of tobacco, alcohol and drugs according to season of last normal menstruation.

# Discussion

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We have confirmed a previous finding of a seasonal variation in the occurence of preeclampsia in Tygerberg Hospital. This was also demonstrated in several other studies reported from over the globe.[80,81] However, in the previous study from this unit data were extracted from daily statistics forms of the department and not from the folders of individual patients as we did in our study. We were certain of the diagnosis of preeclampsia in each patient.

The peak incidence of preeclampsia was during winter with almost one third (32.2%) of all cases occurring during this season. In addition, almost one out of four of all deliveries in winter happened in women with preeclampsia. As before, this was significantly higher than during the summer when only 169 (17.17%) cases of preeclampsia were delivered. This accounted for only 11.48% of all deliveries (1472) during the summer months.

Patients with preeclampsia are a major burden on any health system. They require more frequent and intensive monitoring and management. They develop complications necessitating a longer stay in hospital, often in a high care or intensive care level bed. They often deliver prematurely – either because of maternal complications or placental insufficiency – leading to increased morbidity and mortality for the neonate. All of the above require beds and staff.

By proving that more preeclamptics deliver in the colder winter months, we can prepare ourselves and ensure that sufficient infrastructure is in place to manage this added burden. This can range from temporarily employing more staff – nurses and doctors (paediatricians and obstetricians) - to arranging additional theatre time for

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caesarean sections and increasing our capacity to manage high care patients and prematurely born infants.

As Tygerberg is a referral center, our data and findings can also be used to motivate on a provincial level for the upgrading of the referral system and patient transport services.

An exciting possible application of our results is the counselling of patients at high risk of developing preeclampsia regarding the planning of future pregnancies.

Although the precise aetiology of preeclampsia is still unknown, several risk factors for developing the disease have been identified. Many of them – like age, previous preeclampsia, family members with preeclampsia and medical diseases – cannot be altered. However, one of the few factors that a patient can control (to a certain extent) is the timing of conception.

When we analyzed the data looking at the timing of menstruation (and therefore conception), we found that 292 (29.7%) patients that developed preeclampsia had their last menstrual period in the spring, with November the month of peak incidence. The lowest incidence was found in winter, with only 218 (22.2%) patients.

This is at odds with what Phillips reported from Burlington.[83] Whilst they analyzed only primigravid patients, they found a peak incidence of preeclampsia with conception in the summer months (June through August), with no real difference between autumn, winter and spring.

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Does this mean that we should be counselling patients at high risk of developing preeclampsia that they should try to conceive during the winter months? And if they should fail to conceive during the winter? Should they postpone trying until after the spring or should they wait for a year until the following winter? What about different populations? Rural vs urban? Does ethinicity factor into the equation?

These and other questions have arisen from our research and are still unanswered as data is limited. A large, multi-centre prospective study, looking specifically at the timing of conception and the development of preeclampsia in different populations, could go a long way to establishing guidelines for the counselling of high risk patients.

In the meantime - in the absence of better guidelines - our results should be used at Tygerberg Hospital in the counselling of patients at high risk of developing preeclampsia. We recommend that these patients should try to conceive in the winter months, especially those that have had previous severe, early onset disease.

This brings up the next question – if the onset of disease varies, does that mean that the severity of disease also has seasonal variation? It is not unlikely, as preeclampsia has been characterized by some investigators into 2 different disease entities: early-onset preeclampsia and late-onset preeclampsia. Although the presenting features overlap, they are associated with different maternal and fetal outcomes, biochemical markers, heritability, and clinical features.[91]

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The neonatal (2436.4g ± 929.6g and placental (547.3g ± 184.5g) weights were significantly higher in babies born in the summer. The weights were lowest in those born in the spring - 2153.8g ± 951g and 485.0g ±177.2g respectively. The same level of statistical significance was found when only liveborn babies were considered. There was no difference in five minute Apgar scores < 7 between the seasons of delivery.

When analysing birth weight according to the season of the last menstrual period, we find that the neonatal and placental weights were significantly higher in women whose last normal menstruation was in spring (2335.15g ± 873.2g) or winter (2382.63g ± 820.6g). The lowest weights for neonates (2151.20g ± 906.8g) and placentas (480.4g ± 177.1g) were found in women whose last menstrual period was in the summer. The same level of statistical significance was found when only liveborn babies were considered. Again, no difference was found in the five minute Apgar scores < 7.

The reasons for these differences are unclear. It is most likely related to placental development and the degree of placental insufficiency. It might also be related purely to the slightly more advanced gestational age at the time of delivery in the summer (252.4d ± 29.0d) vs the spring (243.5d ± 31.2d). It would also be interesting to see if the differences in birth weight remains statistically significant in future studies if greater numbers of patients are analysed.

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Further research and long term follow-up of these babies is needed to ascertain whether this increase in birth weight does indeed equate to a decrease in morbidity and mortality and a better outcome overall.

It is important to note that we managed to determine the gestational age at delivery (and therefore the last normal menstrual period and timing of conception) accurately in only 66% of cases. This is a common problem in obstetrics in Southern Africa, especially in the lower socio-economic groups. There are multiple reasons for this, with a lack of education and resources being amongst the most prominent. Whilst this does allow for a certain amount of bias in our study, the same trends were found when analyzing the entire group of preeclamptic patients as when only those with certain gestation was analyzed.

Expectant management – as defined in Tygerberg Hospital – is offered selectively to patients who present with early onset severe preeclampsia. They are managed exptectantly with the aim of improving fetal outcome by increasing the gestational age of the fetus at delivery. To ensure the safety of the mom, the patient is evaluated twice daily for any progression of disease and biochemistry is checked twice a week. The fetus is given a course of antenatal steroids (betamethasone) and qualifies for 6-hourly CTG-monitoring, as well as weekly growth scans and full Dopplers. Where patients gain more than 7 days, a second half course of steroids is usually given.

This management was offered to 11.5% of all patients that presented with preeclampsia. Note that our data does not allow for the analysis of why only this small percentage of patients qualified for expectant management.

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There was no difference in the management during different seasons (expectant vs "stabilise and deliver") based on the timing of delivery, nor was there any difference in the amount of days gained in one season over another when expectant management was attempted.

However, significantly more women were offered expectant management when their last menstruation was during the autumn months (19.90%). They also successfully gained the most days when offered expectant management – a median of 12.5 days. Comparably, those who last menstruated during winter had the lowest number of cases managed expectantly (9.17%), with those whose last menstrual period fell in summer gaining the least number of days (median of 7.5) with expectant management.

There was a statistically significant difference in the medication prescribed for the management of patients with preeclampsia. This held true when data was analysed based on both the timing of delivery and the timing of conception. The reasons for this are unclear. It might be due to the rotation of new interns starting in the department every four months or ther availability of one agent over another. Some doctors favour certain drugs as a matter of personal preference. It might also be linked to the severity of disease, although more evidence is needed to confirm this.

When analising the data based on timing of delivery, it is evident that nifedipine was the drug that was used most often (90.4%). This makes sense, as it is our first-line agent in the management of acute severe hypertension – systolic blood pressure greater than 160mm Hg or diastolic pressure greater than 110mm Hg. It is interesting

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to note that only 68% of patients needed this drug in the summer months, while the incidence was greater than 90% in all three of the other seasons – peaking at 97.9% in the spring. Spring was also the season in which most of our patients required labetalol (23.1%) – our intravenous agent for the management of acute severe hypertension not responding to oral agents.

More patients received methyldopa (our first-line maintenance therapy) – 53.8%, with peak incidence in the autumn (64%) - than nifedipine XL (our second-line maintenance therapy) – 42.8%., with peak incidence in the summer (51.5%). Almost a third of patients (30.8%) required magnesium sulphate, with 41.5% needing it in the springtime. We did not analyse how many patients needed more than one agent to control their blood pressure or whether patients were changed from one drug to another, and if so, for what reason.

Looking at the season of last menstruation, it appears that methyldopa is now the agent most often prescribed, with peak incidence in the winter. Nifedipine and nifedipine XL seem to have an almost identical distribution, peaking in the autumn months. Both labetalol and magnesium sulphate peaked in the summer.

There was no difference in the number of successful inductions in each season based on either the date of delivery or the date of last menstrual period. However, in both instances the method used in the different seasons showed statistical significance. Note that when inductions failed to establish labour, or where patients developed fetal distress, these cases were analysed under causes for caesarean section.

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When analysing the data using timing of delivery, we found that both misoprostol (44 cases) and the artificial rupture of membranes followed by the use of oxytocin (48 cases), were most commonly used in winter. Prepidil was most commonly used in the summer, with 24 cases.

Looking at the timing of last menstruation, both misoprostol (43 cases) and artificial rupture of membranes (25 cases) now favoured those whose last menstrual period was in the spring. Prepidil (27 cases) was now mostly used for those whose last period was in the autumn.

The incidence of caesarean section did not favour a specific season, nor was there any significant seasonal variation in the indication for caesarean section. This was true regardless of whether data was analysed using timing of delivery of timing of last menstrual period.

Every patient admitted with preeclampsia had the following biochemical tests done – serum urea, creatinine, haemoglobin and platelet count. Where the platelet count suggested HELLP-syndrome, AST and LDH were also requested. Patients that qualified for expectant management also had their daily urine protein quantified in g/24hr.

The mean creatinine values were significantly highest in autumn (83,91mmol/l), with the lowest values recorded in spring (64.46mmol/l). None of the other biochemical tests differed between the seasons. None of the laboratory results were influenced by the season during which the last menstruation took place.

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Where possible, patients that present with preeclampsia to Tygerberg Hospital routinely get at least an umbilical artery doppler to assess the placental function (verwysing oor belang daarvan). In those that qualify for expectant management, we also evaluate the uterine arteries to look for notching, as well as the ductus venosus. In our study we found no statistically significant differences in the distribution of Doppler results in the different seasons for either the timing of delivery or the timing of last menstrual period.

The final aspect that we evaluated was the rate of complications experienced by patients with preeclampsia. These included, but were not limited to, the following: eclampsia, HELLP syndrome, pulmonary embolism, intra-cranial haemorrhage, liver failure, renal injury/failure, ascites, placental insufficiency, intra-uterine demise and abruptio placentae. These complications are extremely relevant, as preeclampsia remains one of the leading causes of maternal, fetal and neonatal morbidity and mortality – accounting for 10 – 15% of direct maternal deaths worldwide. At Tygerberg Hospital, 3 out of 17 maternal deaths in 2010 were due to preeclampsia.

Neither the season of delivery nor the season of last menstruation had any statistically significant impact on the distribution of the complications of preeclampsia.

These results, along with the limited seasonal variation in biochemical markers and the absence of significance in the seasonal variation in Doppler flow, strongly suggest that there was not any significant variation in the severity of disease diagnosed during the different seasons.

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# CONCLUSION

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Our study has again proven that there is indeed a seasonal variation in the incidence of preeclampsia. We have gone one step further and proven that this variation is not just based on the timing of delivery, but that preeclampsia also varies according to the season during which the last menstrual period (and therefore conception) takes place.

The reasons for this are still unknown, but theories suggest it is linked to the seasonal change in plasma volume experienced. Other possible causes include dietary changes and increased rate of infections during the winter months.

The implications of these results need to be analysed further. In essence, they could be used to motivate for the appointment of additional personnel to manage the increased patient load experienced during the winter. They might also be used to advise patients at high risk of developing preeclampsia to try and conceive during the winter months or that their chance of developing preeclampsia is greatest if they conceive in the spring.

Lastly, we feel that this study has shown that further studies on this subject could prove invaluable. A large, multicenter, prospective trial, analysing the degree of hypertension and taking an in depth look at the outcomes for both the patients and their babies could give valuable information that might change our management of this global disease.

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