

Urinary Porphyrins and Porphyrin Precursors in Normal Pregnancy

RELATIONSHIP TO URINARY TOTAL OESTROGEN EXCRETION

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SUMMARY

The relationship between urinary excretion of porphyrins, porphyrin precursors and total oestrogens in normal pregnancy was investigated. Significant increases in total oestrogen, delta-aminolaevulinic acid (ALA) and coproporphyrin (COPRO) excretion were noted. However, no close correlation was found between total oestrogen excretion and urinary output of ALA and COPRO. The results suggest that the observed increases in ALA and COPRO excretion during pregnancy may not simply be the result of steroid-mediated induction of hepatic haem biosynthesis, as has been proposed.

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It has long been suspected that certain endogenously produced steroid hormones may play an important role in regulating hepatic haem biosynthesis. The evidence is both circumstantial and experimental. Various authors have stressed the importance of endocrine factors in the precipitation of attacks of acute intermittent porphyria (AIP). Thus, the preponderance of females over males presenting with symptoms and signs of this disease is well recognised;^{1,2} it is uncommon for the disease to become manifest before puberty,² and exacerbations in association with the menstrual cycle and with pregnancy have been noted.^{3,4} Furthermore, administration of sex hormones both to patients with AIP and variegate porphyria (VP) has frequently been reported to lead to biochemical and clinical deterioration.⁵⁻⁸ On the experimental side, a number of endogenously produced steroid metabolites have been shown to be capable of strongly stimulating porphyrin biosynthesis in chick embryo liver cell cultures^{9,10} and of increasing hepatic delta-aminolaevulinic acid (ALA) synthetase activity in rats.¹¹

Recently, it has been claimed that urinary excretion of ALA, porphobilinogen (PBG), coproporphyrin (COPRO) and uroporphyrin (URO) is significantly increased in normal pregnancy.¹² In view of the abovementioned associations, the increases were attributed to the increased steroid hormone production in pregnancy, but no direct

evidence on this aspect was adduced. We report here the results of an investigation into the relationship between urinary excretion of porphyrins, porphyrin precursors and total oestrogens in normal pregnancy.

MATERIAL AND METHODS

Serial weekly determinations of urinary total oestrogens as well as of ALA, PBG, URO and COPRO were performed on 24-hour urine specimens from 7 healthy women during the last 12 weeks of pregnancy. Determinations were also performed for 2 weeks after delivery. None had a family history of porphyria, or clinical or biochemical evidence of liver disease. Urine specimens were stored in dark containers at -20°C until analysis, which was always within 2 days of collection. Total oestrogens were determined by the method of Oakey *et al.*¹³ Urine was analysed for ALA and PBG according to Mauzerall and Granick¹⁴ and for COPRO and URO according to Rimington.¹⁵ Urinary creatinine was determined by the method of Larsen.¹⁶

Statistical analysis of the results was carried out as follows: the period of study was divided into two phases: (1) 29th to 34th week, and (2) 35th to 40th week. For each of the substances determined a mean value was calculated for phase 1 and compared with the mean for phase 2 by means of Student's *t* test. In addition, the mean increase or decrease in each parameter for the period 29 - 40 weeks, and for phases 1 and 2 was determined graphically and compared with zero by means of Student's *t* test.

RESULTS

The results are depicted in Fig. 1. Mean urinary excretion of total oestrogens, ALA, and COPRO was found to be significantly higher during phase 2 than during phase 1 ($P < 0.05$). Following delivery there was a marked fall.

There was a statistically significant increase in urinary total oestrogen excretion during the period 29 - 40 weeks ($P < 0.01$). Furthermore, this was found to be true for the mean increases during both phase 1 and phase 2 ($P < 0.05$).

The mean increase in urinary ALA excretion during the period of study also proved to be significant ($P < 0.05$). However, separate analysis of the results in phase 1 and phase 2 showed that the significant increase occurred during the first part of the study ($P < 0.05$). There was no significant increase or decrease in phase 2. It is noteworthy that the absolute increase in ALA excretion is modest, and

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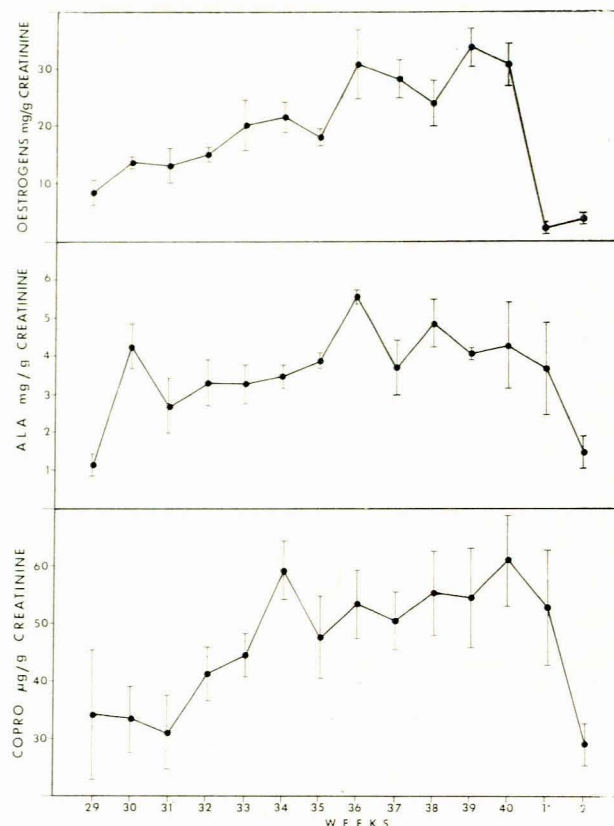


Fig. 1. Mean (\pm SE) urinary oestrogen, ALA and COPRO excretion in normal pregnancy (third trimester) and after delivery (\times = postpartum).

in fact the highest values recorded still lie within the normal range.¹⁷

In the case of COPRO the findings were essentially the same as those for ALA, i.e. there was a significant over-all increase in urinary COPRO excretion ($P < 0.01$) which occurred during the first phase of the study ($P < 0.05$). As with ALA the absolute increase in mean COPRO excretion was modest and the highest values found were not outside the normal range.¹⁷

No significant increase or decrease in PBG excretion was observed at any stage of the study. The same was found for URO.

DISCUSSION

The results of the present study confirm in part the findings of Lyberatos *et al.*¹² They reported a significant difference in urinary excretion of ALA, PBG, URO and COPRO between pregnant and non-pregnant subjects. In contrast, we found that only urinary ALA and COPRO excretion increased significantly in the third trimester and decreased after delivery. These differences may, therefore, be due to the different approaches used in the two studies.

In the present investigation oestrogen excretion increased significantly throughout the period of study up to term, whereas the significant increase in ALA and COPRO excretion occurred during the first half of the study.

This suggests, but does not, of course, prove, a dissociation between oestrogen production and the formation of porphyrins and their precursors.

If it is assumed that the increases in ALA and COPRO excretion in the present study were due to increased steroid hormone production, how can the apparent discrepancies be explained? There are several possibilities. It could be that hepatic haem biosynthesis is maximally stimulated by the plasma concentrations of oestrogens already prevailing at the 34-week stage of pregnancy and that further increases in the production of these steroids has, therefore, no additional effect. Alternatively, it may be that a closer correlation might be demonstrable between the urinary output of one or other individual oestrogen and urinary excretion of ALA and COPRO. Thirdly, it may be that steroids other than oestrogens are more important in this context. In the liver cell culture system certain C_{19} and C_{21} steroids of the 5β -H type, including etiocholanolone, pregnanediol, 11-ketopregnanolone and pregnanetriol, were found to be the most active in inducing porphyrinogenesis.^{9,10}

Other considerations indicate that the observed increases in urinary ALA and COPRO excretion during pregnancy may not simply be the result of steroid-mediated induction of hepatic ALA synthetase, the rate-controlling enzyme for liver haem biosynthesis: (i) numerous factors besides steroid hormones are known to be capable of influencing porphyrin metabolism and urinary excretion of porphyrins and por-

phyrin precursors;¹⁸⁻²¹ (ii) in the present study no significant increases in urinary PBG or URO excretion could be demonstrated; (iii) oestrogens are well known to impair hepatic excretory capability²² which could account at least for the increase in urinary COPRO excretion; (iv) recent evidence from studies on rats suggests that hepatic ALA synthetase is in fact less inducible than usual during pregnancy.²³

It would seem, therefore, that much further work is required to clarify the exact part played by oestrogens and other steroids both with regard to the physiological control of hepatic haem biosynthesis and with regard to the pathogenesis and exacerbation of the hepatic porphyrias.

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Radiologiese Diens by Tygerberg-Hospitaal

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SUMMARY

The Tygerberg Hospital, of the Medical Faculty of the University of Stellenbosch, has a decentralised radiological service where 50% of the radiology forms part of specialised departments. This obviates patient traffic and ensures an efficient technical service and close collaboration between the radiologist and the specialist concerned. The main department, when finally completed in a few years' time, will have 24 diagnostic rooms for general and special purposes and about 30 decentralised rooms.

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Die geografiese ligging, klimaatsomstandighede, finansiële en gebruiksfaktore bepaal die ontwerp van enige publieke gebou in enige deel van die wêreld — dit geld ook vir hospitale.

Die radiologiese afdeling kan as 'n sentrale eenheid in die hospitaalkompleks beskou word wat 'n diens aan alle kliniese departemente verskaf, gebruik word deur alle soorte van pasiënte in verskillende stadia van siekte, en bedien word deur administratiewe, tegniese, verplegings- en mediese staf, wat as een span moet saamwerk.¹

Hierdie departement moet sentraal geleë wees maar moet rekenskap hou met toekomstige uitbreiding wat betref apparaat en verbeterings, en dus moet die ontwerp buig-

saam wees sonder om later groot strukturele bouveranderinge te benodig.

Die Tygerberg-hospitaal, met 2 000 beddens en 'n groot buitepasiënte-afdeling vir Blank en nie-Blank, sal teen 1975 'n minimum van 250 000 radiologiese ondersoeke per jaar moet doen en met 'n toename van 10% per jaar bereken — wel 500 000 ondersoeke teen 1983. Een-derde sal binnepasiënte wees en twee-derdes buitepasiënte, met gelyke fasiliteite vir Blank en nie-Blank. Aanpassing moet maklik kan geskied in noodgevalle.

Wheeler² se formule om die getal radiologiese kamers te bepaal is taamlik ingewikkeld maar kom op die volgende berekening neer: algemene radiografiese diens benodig 30 gevalle per dag per kamer; deurligtingskamers beskikbaar vir spysverteringskanaalwerk, 15; ander tipe ondersoeke soos urologiese radiologie, 10; en spesiale arteriële en neuroradiologie, 6 gevalle per dag. Rekenskap moet ook gehou word met die spesiale vereistes van 'n opleidingskompleks waar ingewikkelde prosedures wat net 3% van alle ondersoeke uitmaak wel 25% van die beskikbare tyd in beslag neem.

Die getal radiografiese kamers by Tygerberg-hospitaal sal uiteindelik meer as 50 wees, waarvan 24 die sentrale diens verskaf op die 4de verdieping van buitepasiënte, blok C. Die res van die departement is gedentraliseer op verskeie verdiepings, vanaf die 1ste tot die 8ste.

Basies is daar drie stadia van 'n radiologiese diagnostiese diens: (i) om die pasiënte by die X-straalkamer te kry, (ii) die tegniese prosedure en filmontwikkeling, en (iii) konsultasiediens van die radioloog. 'n Verdere stadium kan bygerekend word as die klassifikasie van die films vir

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