Journal of
Clinical Medicine

MDPI

Editorial

Pregnancy and Kidney Diseases: Multidisciplinary Follow-Up and the Vicious Circles Involving Pregnancy and CKD, Preeclampsia, Preterm Delivery and the Kidneys

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1. Introduction

Thomas Addis, the father of nephrology, once wrote that a clinician is complex, "he is part craftsman, part practical scientist, and part historian" [1]. It is in fact in history that we often find insights that enable us to interpret the times in which we live. Reflecting on the many unsolved issues mentioned in the previous editorial [2], we would like to draw the reader's attention to the circular nature of the relationship between kidney and pregnancy and to two vicious circles, the focus of two extraordinary papers, one published at the beginning and one at the end of the 20th century [3,4].

2. From CKD to Preeclampsia and Back

Pregnancy complications affect the kidney and kidney diseases affect pregnancy complications (Figure 1). The lecture entitled "The albuminuria of pregnancy and the kidney of pregnancy", which was published in The Lancet on 23 December 1905 [3] (Figure 2) deals with five emblematic cases. The first was a 42-year-old woman, at her sixth pregnancy, who complained of mild visual blurring and oedema in her seventh month of gestation; mild hypertension was found, and after a phase of oliguria/anuria, with increased proteinuria, symptoms disappeared with the delivery of a child dead in utero. The second case, a primiparous, 23-year-old woman, with eclampsia at five months of gestation, died after the delivery of twins, dead in utero. This case allows the author to discuss the differential diagnosis, which he analyses as follows: "When you discover albumin in the urine of a pregnant woman you must bear in mind that it may be due to three very distinct conditions. The patient may be the subject of acute nephritis or acute Bright's disease; she may be suffering from chronic nephritis aggravated by the pregnancy, or she may be suffering from the albuminuria of pregnancy and the so-called kidney of pregnancy which [omissis] does not correspond quite to any of the varieties of acute nephritis or acute Bright's disease" [3]. In the third case, a young woman, with a history highly suggestive of Bright's disease, the "toxemic theory" supported the idea that albuminuria is caused by the action of "certain toxins" circulating in the mother's blood [3]. The woman died of uraemia after delivering a child in the eighth month of pregnancy. In the fourth case, with a similarly grim prognosis, the woman had a small shrunken kidney, probably from "chronic pyelonephritis". The questions the author posed still hold true: "What dangers does the kidney of pregnancy expose the patient to?" His answer is that "They are mainly three in number: first of all there is eclampsia, which occurs in about one in every five cases of the kidney of pregnancy; secondly, there is the subsequent development of chronic nephritis; and thirdly, the danger of partial or complete loss of vision due to the changes in the eye. Another danger that will occur to you is that of uraemia but when this takes place the case

Citation: Piccoli, G.B.; Attini, R.; Torreggiani, M.; Cabiddu, G. Pregnancy and Kidney Diseases: Multidisciplinary Follow-Up and the Vicious Circles Involving Pregnancy and CKD, Preeclampsia, Preterm Delivery and the Kidneys. *J. Clin. Med.* **2022**, *11*, 2535. https://doi.org/10.3390/jcm11092535

Received: 24 April 2022
Accepted: 29 April 2022
Published: 30 April 2022

is more likely to be one of acute nephritis or acute Bright's disease than of the kidney of pregnancy" [3].

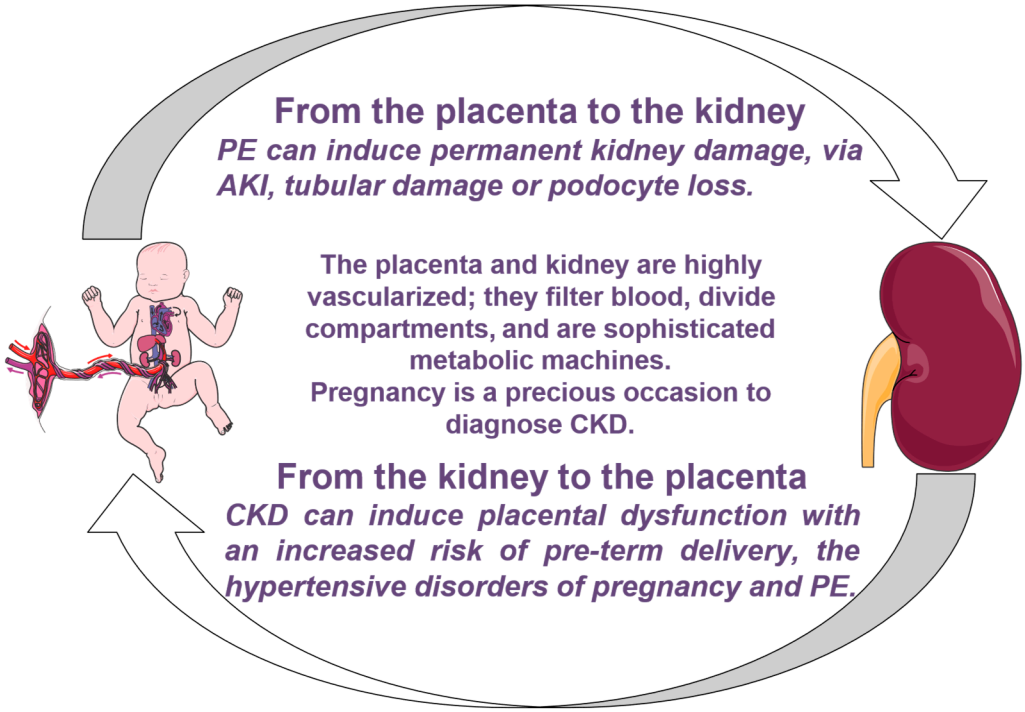

Figure 1. The vicious circle from the placenta to the kidney and from the kidney to the placenta. Adapted from [5]. PE: preeclampsia, AKI: acute kidney injury, CKD: chronic kidney disease.

Further on, the author considers the long-term dangers, and the risks of recurrence of the "kidney of pregnancy", stating that this is presumably higher in cases that occur early during gestation. Likewise, the higher risks of adverse pregnancy outcomes in women with Bright's disease, which, at the time, encompassed all chronic diseases of the kidneys, in the absence of imaging and well before kidney biopsy became available, were underlined, together with the difficulty in discriminating during, and often even after, pregnancy between "kidney of pregnancy" and Bright's disease.

One hundred years later, we know more about this first vicious circle (Figure 1) from the diseased kidney to the placenta and from the placenta to the diseased kidney. Recent studies highlight the fact that the circulating biomarkers recognized by Blacker have distinct behaviours in preeclampsia, chronic kidney disease (CKD) and superimposed pre-eclampsia [6,7]. Furthermore, all forms of early CKD are now acknowledged to be associated with higher risks of adverse pregnancy outcomes, and this holds true even for "trivial" conditions, such as a history of nephrolithiasis, previous acute kidney injury (AKI) or Stage 1 CKD [8,9]. With this in mind, several groups, including ours, strongly advocate that serum creatinine be included among the tests routinely prescribed at the start of pregnancy or in pre-gestational assessment [10]. If we knew more about the effects even initial CKD or a "healthy" reduction in kidney tissue (e.g., kidney donation), have on a subsequent pregnancy, we could obtain additional information on the detrimental association between preeclampsia, other hypertensive disorders of pregnancy and future maternal cardiovascular and kidney health [11].

THE LANCET, DECEMBER 23, 1905.

A Lecture
ON
THE ALBUMINURIA OF PREGNANCY AND THE KIDNEY OF PREGNANCY.

Delivered at University College Hospital on Nov. 8th, 1905,

BY G. F. BLACKER, M.D. LOND.,
F.R.C.P. LOND., F.R.C.S. ENG.,
OBSTETRIC PHYSICIAN TO THE HOSPITAL AND TO THE GREAT NORTHERN HOSPITAL.

GENTLEMEN,—I have chosen for my lecture to-day the subject of the albuminuria of pregnancy and the kidney of pregnancy on account of their important relation to eclampsia and because recently I have had under my care in the hospital a typical case of this condition. The details of the case are as follows.

CASE 1.—A patient, register No. 1773, aged 42 years, 5-para, was sent into the University College Hospital on Sept. 7th, 1905, by Mr. W. S. Rooke of Finchley. She was seven months pregnant and was complaining of dimness of vision, slight œdema of the legs, and frequency of micturition. The œdema had been present a month and the frequency of micturition and dimness of vision for about a fortnight. She had previously been a perfectly healthy woman and had had five normal pregnancies and confinements, the last having occurred nine years ago. On admission the pregnant uterus was found to reach up to a height of seven and a half inches above the symphysis pubis and there was slight œdema of both ankles. The arterial tension was a little raised but the heart was normal. The urine was acid, normal in colour, contained $\frac{1}{16}$th albumin, and hyaline, granular, and a few epithelial casts. The specific gravity was 1012 and the amount passed in the first 24 hours was 48 ounces. On admission the patient was placed upon a strict milk diet and ordered half a drachm of pulvis jalapæ compositus every morning. Two days after admission my colleague, Mr. Percy Flemming, kindly examined the eyes and found the following conditions present. There were numerous white areas of exudation in each fundus, also numerous flame-shaped hæmorrhages and slight neuritis. There were no signs of old-standing disease. Vision: right eye, J.19; left eye, J.16. As vision appeared to be failing rapidly he strongly recommended the induction of premature labour. On Sept. 11th, four days after admission, the amount of urine passed in the 24 hours was 17 ounces (some being lost); it contained $\frac{1}{16}$th albumin, 1·15 per cent. urea, and had a specific gravity of 1012. At 8 P.M. of this day two bougies were introduced into the uterus and on the 12th, 16 hours after the introduction of the bougies, the patient was delivered of a dead child 15 inches in length. From this time her improvement was most marked. On the 13th 26 ounces of urine were collected in the 24 hours; it contained $\frac{1}{16}$th albumin and the urea had increased to 2·75 per cent. Vision had improved to J.12 right eye and J.4 for letters left eye. On the 18th the urine contained merely a trace of albumin and on microscopical examination no casts but a few pus cells were found. On the 19th her sight was tested again and found to be J.1 for either eye. Involution of the uterus occurred normally and the temperature did not rise above 99·6° during her stay in the ward. On the 20th Mr. Flemming again examined her eyes and found that the exudation was rapidly breaking up and becoming absorbed in both eyes. The patient's general condition continued to improve and on Oct. 9th she left the hospital, the urine now containing only a faint trace of albumin. On Nov. 4th she was again seen by Mr. Flemming and he found the vision of each eye normal; there was no neuritis and the soft-edged white patches of exudation had disappeared. Between the disc and the macula were several small, bright, well-defined spots. On the 7th an examination of her urine showed that it was acid, containcd $\frac{1}{24}$th albumin, and 1·7 per cent of urea. There were no casts on microscopical examination. The specimen was not, however, a mixed one of the 24 hours' urine and the patient was taking practically an ordinary diet, except that she was eating very little meat.

This case is, I think, a good example of the albuminuria of pregnancy, no doubt due to the so-called kidney of pregnancy. The great importance of such a case lies in the fact that if the condition is not recognised and properly treated eclamptic convulsions are very likely to develop. As you all know, eclampsia is one of the most dangerous complications of childbirth. It is attended with a maternal mortality of from 20 to 30 per cent. and a fœtal mortality of from 40 to 50 per cent. or even more. In the Registrar-General's report for 1903 409 deaths are attributed to puerperal convulsions and if we estimate the mortality at 20 per cent. some 2045 cases occurred during that year in England and Wales. I do not, however, propose to discuss eclampsia to-day but a condition which undoubtedly predisposes to it and not infrequently precedes it—namely, the albuminuria of pregnancy and the so-called kidney of pregnancy. Dührssen found albumin in the urine in 96 per cent. of his cases of eclampsia. A small percentage of cases possibly occurs in which there is no albumin in the urine but eclampsia is a disease the exact nature of which still remains to be discovered and we are yet uncertain whether the primary lesion is one of the liver or of the kidneys. If the liver plays the important part attributed to it by some writers on eclampsia then it is not surprising that cases are met with from time to time in which no albumin is found in the urine.

Herman has shown that pregnant women are about fourteen times more liable to acute kidney diseases than are non-pregnant women of a corresponding age and this was the view held by the older pathologists. In 1886, however, Leyden drew attention to the fact that the pathology of the so-called kidney of pregnancy does not correspond to that of acute nephritis or acute Bright's disease as we generally see it. He pointed out that the kidney of pregnancy is slightly enlarged, its capsule is a little adherent, the cortex is markedly anæmic, while there is usually slight congestion of the medulla, and on microscopical examination there is some fatty infiltration, as he termed it, of the epithelium, more especially that lining the convoluted tubules. I have here a kidney of a woman who died from eclampsia and you see it is a little enlarged; there is marked anæmia of the cortex, with some congestion of the medulla. Microscopic sections show that the epithelium of the tubules is somewhat compressed by an exudation into their lumen but there are no fatty changes in the epithelium and the vessels are healthy and present in their normal number, although the cortex is so markedly anæmic. The liver from the same case shows numerous patches of necrosis scattered throughout its substance round the smaller portal vessels, with destruction of the liver cells. Practically the whole of the post-mortem changes found in this case were in the liver, and the kidneys, except that the cortex was markedly anæmic, were hardly affected at all. Indeed, as you see, the kidneys in this patient dying from eclampsia are a good example of the condition described by Leyden as the kidney of pregnancy, except that there is no fatty degeneration of the epithelium. The details of the case are as follows.

CASE 2.—The patient, Register No. 43, a primipara, 23 years of age, was admitted into University College Hospital in December, 1903, under the care of Dr. Herbert R. Spencer. She was five months pregnant and was suffering from eclamptic convulsions. She was treated by morphia, the cervix was fully dilated by Bossi's dilator to 11 centimetres, and dead twins were extracted. The patient, however, died eight hours after delivery, having had 22 fits in 30 hours. At the post-mortem examination the conditions which I have described to you were found in the liver and the kidneys.

In discussing the question of albumin in the urine in pregnancy you must remember there are three main causes for its presence. Albumin is found in cases of congestion of the kidneys, in cases of toxic poisoning, and in cases of true Bright's disease, the so-called renal albuminuria.

Before I proceed to discuss the causation of the presence of albumin in the urine in pregnant women I will consider the frequency of its occurrence. Statistics on the point are very divergent and that is because not all the observers have employed the same tests for the recognition of the albumin. Some have included cases in which only a mere trace of albumin was found on careful chemical examination, while others have counted only those cases in which the amount of albumin was of pathological importance. Bumm estimates that albumin can be found in the urine of about 10 per cent. of pregnant women if it is examined daily over long periods of time and if mere traces of albumin be

Figure 2. The front page of the paper "The albuminuria of pregnancy and the kidney of pregnancy", *The Lancet*, 23 December 1905 [3].

We still need, however, to cast light on the effect of the different kidney diseases on pregnancy, to try to better understand whether quantity or quality of tissue counts, and to determine what effect specific diseases have on pregnancy outcomes. Is the relationship between the hypertensive disorders of pregnancy and subsequent kidney health an effect of hypertensive and proteinuria insult to kidney tissue? Is this effect mediated by loss of podocytes, or is it the reflection of a pre-existent kidney disease, now found in at least 20% of cases when searched for, or is it the first sign of a subclinical kidney injury, for example

in the case of obesity [8]? We hope that some of these questions will be answered in the present issue.

3. Being Born Small and the Risk of Having Small Babies

The second paper that we would like to comment on appeared in Epidemiology in 1999 [4]. Written nearly a decade before the pivotal paper by Vikse and his colleagues was published [12], its title not only highlights the importance of preeclampsia in the future development of CKD, but also demonstrates awareness of the second kidney-related vicious circle in pregnancy: small, or preterm babies, who have, in turn, a higher risk of complicated pregnancies, and of giving birth to small babies.

According to this study, being born small, and as we now better acknowledge, small for gestational age, increases by 4 to 6 times the risk of having a complicated pregnancy, leading in turn to an increased risk of giving birth to a "small baby" [4].

In more recent studies, being born small for gestational age has increasingly been associated with the development of hypertension, metabolic syndrome and kidney disease in adulthood [13–15]. Indeed, we now know that the slow, and sometimes unpredictable, maturation of the kidney tissue is probably one of the reasons for this increased risk, and may also be the mediator of the increased risk of the hypertensive disorders of pregnancy observed in the pregnancies of women born small, preterm, or small for gestational age [14] (Figure 3).

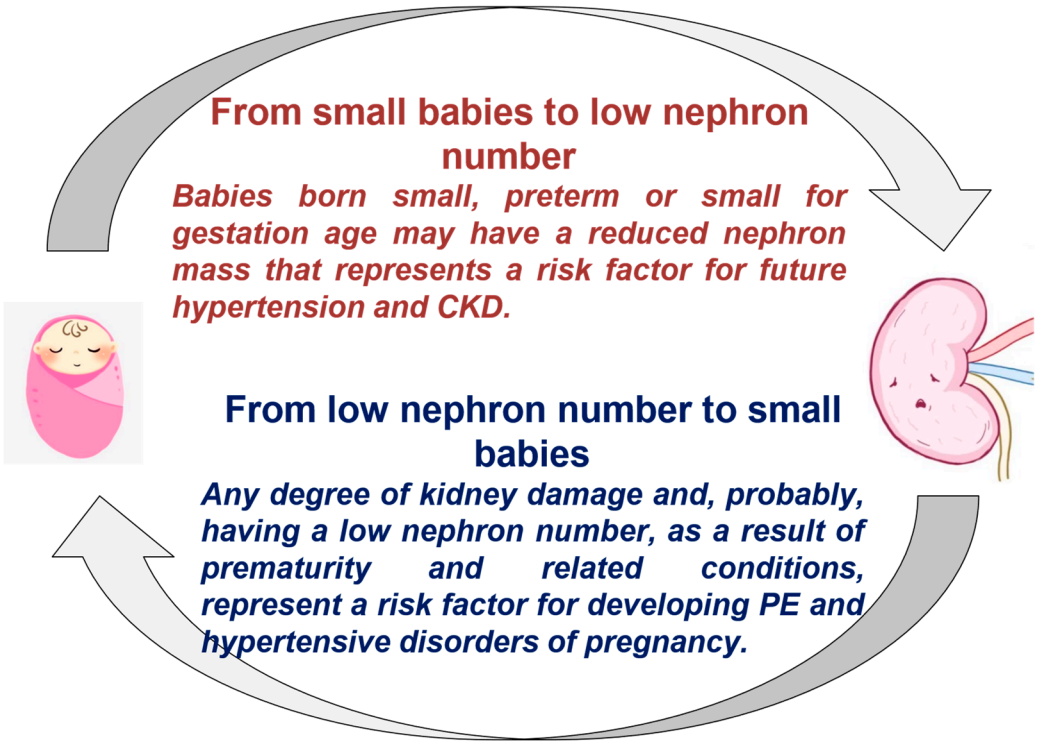

Figure 3. The vicious circle from small baby to complicated pregnancy and back to small baby. PE: preeclampsia, CKD: chronic kidney disease.

Once more, even though our knowledge of these interrelated events has increased enormously in recent years, being born small (in all its variants) is not considered a significant risk factor for the development of the hypertensive disorders of pregnancy, or included in counselling. The vast and fascinating field of epigenetics is open for discussion, while, possibly because of the heterogeneity of the hypertensive disorders of pregnancy, what constitutes a favouring genetic background remains unknown.

While shedding light on these and other open issues, including parenthood, is quite an ambitious task, we hope that our series will contribute to the field, adding one more drop to the ocean and creating a butterfly effect.

Author Contributions: Conceptualization, G.B.P.; writing—original draft preparation, G.B.P., R.A., M.T. and G.C.; writing—review and editing, G.B.P., R.A., M.T. and G.C. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflict of interest.

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