Obstetric Nephrology: Pregnancy in Women with Diabetic Nephropathy—The Role of Antihypertensive Treatment

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Summary
This review highlights factors of importance for the clinical care of pregnant women with pregestational diabetes and microalbuminuria or diabetic nephropathy with particular focus on the role of intensive antihypertensive treatment during pregnancy. Most information in the literature comes from women with type 1 diabetes and diabetic nephropathy, but this is probably also valid for women with type 2 diabetes. Careful counseling of women with diabetic nephropathy before pregnancy with estimation of the risk for the mother and fetus is important. Pregnancy does not result in worsening of kidney function in women with diabetic nephropathy and normal serum creatinine, but pregnancy complications such as pre-eclampsia and preterm delivery are common. Intensive metabolic control before and during pregnancy, low-dose aspirin from 12 gestational weeks onward, and intensive antihypertensive treatment are important. Methyldopa, labetalol, and nifedipine are regarded safe in pregnancy, whereas angiotensin converting enzyme inhibitors, AngII antagonists, or statins should be paused before pregnancy. Case series and pathophysiological studies support the use of a stringent goal for BP and albumin excretion in pregnant women with diabetic nephropathy. Screening for diabetic retinopathy before and during pregnancy is mandatory and laser treatment should be performed if indicated. Pregnancy outcome in women with diabetic nephropathy has improved considerably with a take-home-baby rate of approximately 95%. Further research on the benefits and risks of intensive antihypertensive treatment in this population is needed.


Introduction
Pregnancy in women with type 1 or type 2 diabetes is associated with a two- to four-time increased risk of pre-eclampsia, preterm delivery, and perinatal mortality compared with the background population (1). For many years, type 1 diabetes was the most common type of diabetes in pregnancy; however, with increasing prevalence of type 2 diabetes in women of childbearing age, an increasing number of pregnant women with type 2 diabetes is seen.

In an unselected population of women with type 1 diabetes, diabetic nephropathy is present in up to 7% (2). Diabetic nephropathy in those with type 2 diabetes is also seen but is less frequent, and to our knowledge this has not been described in the literature. Diabetic nephropathy is probably the most common CKD seen in pregnancy.

For many years pregnancy in women with diabetic nephropathy was associated with an even higher risk of pregnancy complications including perinatal mortality and the risk of decline in maternal kidney function leading to ESRD (3). However, maternal and perinatal mortality and morbidity rates in pregnancies with diabetic nephropathy have declined substantially during the last decade. Successful pregnancy outcome with fetal survival rates of up to 95%–100% is now the norm in developed countries (4–11). Nonetheless, even with the best clinical care, maternal and perinatal complications in women with diabetic nephropathy are still more common than in women with normal urinary albumin excretion at conception. Furthermore, there are concerns regarding the possible short- and long-term effects on maternal and infant morbidity and mortality.

This literature review highlights factors of importance for the clinical care of pregnant women with pregestational diabetes and microalbuminuria or diabetic nephropathy with particular focus on the possible role of strict antihypertensive treatment during pregnancy. The majority of data on this topic are from women with type 1 diabetes. Most likely, the findings are similar in women with type 2 diabetes and the clinical recommendations given in this literature review are probably useful in both type 1 and type 2 diabetes.

Pathophysiology and Treatment of Diabetic Nephropathy
Diabetic nephropathy is a progressive disease that affects approximately 30% of patients with diabetes and is the most common cause of ESRD in the United States. In Denmark, 22% of patients with ESRD have diabetes (12). The first clinical sign is microalbuminuria, defined as a urinary albumin excretion of 30–300 mg/24 h, corresponding to a spot urine albumin/creatinine ratio of 30–300 μg/mg. Left untreated, microalbuminuria tends to progress to overt diabetic
nephropathy characterized by persistent proteinuria, hypertension, and a relentless decline in GFR (13). Histologic changes in the glomeruli with increased basal membrane thickness and glomerulosclerosis are characteristic. Progression to ESRD occurs with a median duration of 7 years after onset of diabetic nephropathy, but renin angiotensin system (RAS) inhibition in combination with other antihypertensive agents has improved the prognosis considerably. Progression of diabetic nephropathy can be slowed by intensive antihypertensive treatment with angiotensin converting enzyme (ACE) inhibitors or angiotensin II (AngII) receptor antagonists as first-line drugs (14–16). It is often necessary to combine this treatment with diuretics, β-blockers, and/or calcium antagonists to sufficiently control the BP and the albumin excretion. Intensive antihypertensive treatment in patients with diabetic nephropathy results in preservation of kidney function documented by a reduction in the decline in GFR to less than one-third of the decline in untreated patients (13). Inhibition of the RAS with ACE inhibitors in normotensive patients with microalbuminuria may possibly eliminate albuminuria (17,18). The treatment goal includes BP <130/80 mmHg (19) and lower or normalized urinary albumin excretion.

RAS inhibition is, however, contraindicated in pregnancy and alternative drugs must be used as discussed below.

Effects of Pregnancy on Diabetic Nephropathy

Only a few studies have addressed the long-term effect of pregnancy on renal function in women with diabetic nephropathy. The most recent is a prospective cohort study that included 26 women with diabetic nephropathy and normal serum creatinine followed for up to 13 years with at least one pregnancy during the period, who were compared with women with diabetic nephropathy followed in the same way with no pregnancies in the observation period. The women were offered strict BP control during the whole study period. In women with normal serum creatinine, pregnancy was not associated with a greater decline in kidney function or impaired long-term maternal survival (20). However, other studies report that there is increased risk of deterioration of kidney function during pregnancy in women with a reduced creatinine clearance (5,21,22).

In general, pregnancy outcome is favorable in women with small elevations in serum creatinine <124 μmol/L (1.4 mg/dL), proteinuria <1 g/24 h, and normal BP (23). In contrast, serum creatinine >176 μmol/L and severe hypertension or proteinuria in the nephrotic range (>3 g/24 h) and/or pre-existing cardiovascular disease is associated with a high risk for poor maternal and fetal outcome (23). The long-term survival of a mother with diabetic nephropathy has improved considerably in recent years, but the long-term likelihood of complications including visual impairment and renal dysfunction is still increased (8,10,20).

Pathophysiology of Pre-Eclampsia and Hypertension in Diabetic Pregnancy

Pre-eclampsia is characterized by hypertension, proteinuria, and peripheral edema. Patients with microalbuminuria or diabetic nephropathy before pregnancy are at increased risk of developing pre-eclampsia and may already present with elevated BP in early pregnancy. Among 83 women with type 1 diabetes of >10 years followed prospectively during pregnancy, 14 developed pre-eclampsia (21). They were characterized by higher urinary albumin excretion, BP, and hemoglobin A1c (HbA1c) in early pregnancy compared with women who did not develop pre-eclampsia (Table 1). In the 14 women subsequently developing pre-eclampsia, impaired vasodilatory capacity, as measured by ultrasound at the brachial artery after inducing maximal dilation with nitroglycerin at 11 and 29 gestational weeks, was present at 29 gestational weeks, i.e., before development of pre-eclampsia. In addition, the vascular cell adhesion molecule and intracellular adhesion molecule-1 markers of endothelial dysfunction were elevated (Table 1) (28). Signs of vascular dysfunction thus precede development of clinical pre-eclampsia in women with type 1 diabetes who are prone to the condition. In addition, several other pathophysiological aspects are involved such as increased oxidative stress and reduced antioxidative defenses probably related to levels of vitamin C and E (29,30). However, supplementation with vitamins C and E in a randomized study including 762 women with type 1 diabetes did not reduce the risk of pre-eclampsia (30). As in pre-eclampsia in women without diabetes, pre-eclampsia in women with type 1 diabetes is also associated with elevated levels of antiangiogenetic factors in the third trimester (27).
Pre-Eclampsia and the RAS

During the early stages of normal pregnancy, activation of the local RAS (31,32) and systemic RAS (33,34) exists. At 3–6 gestational weeks, plasma prorenin levels increase 10-fold, with much lower prorenin levels from 9 weeks onward (31). This is consistent with a role for the renin angiotensin system, particularly prorenin, in embryonic and fetal development and in placentation (31). In pre-eclampsia, disturbance in the renin angiotensin system is seen with increased vascular responsiveness to AngII (35). The prorenin levels in 108 pregnant women with type 1 diabetes have been prospectively investigated and higher prorenin concentrations at 8 gestational weeks were associated with later development of pre-eclampsia (36). Likewise, throughout pregnancy, prorenin concentrations were 30% higher in the nine women with type 1 diabetes who developed pre-eclampsia compared with those who did not (36). This may reflect that the first step in the renin angiotensin system is activated very early on in patients with diabetes later developing pre-eclampsia. This observation in pregnant patients with diabetes is in line with the well-documented effect of inhibition of the renin angiotensin system on the progression of kidney involvement in nonpregnant diabetic patients also when only discrete changes are present (17).

Pre-Eclampsia and Vasoactive Markers

The vasoactive marker of cardiac overload atrial natriuretic peptide (ANP) is synthesized in cardiac tissue in response to volume expansion and ventricular pressure overload (37,38). In nondiabetic women, increased levels of ANP and brain natriuretic peptide are seen in late pregnancy when the diagnosis of pre-eclampsia has been established (39,40). In a small, prospective series of women with type 1 diabetes followed throughout pregnancy at our center, pre-eclampsia developed in six women (7%) with significantly higher ANP levels at 9 gestational weeks compared with women not developing pre-eclampsia. Throughout pregnancy, ANP levels were 34% higher in these women (41). As in pre-eclampsia in nondiabetic women, pre-eclampsia in women with type 1 diabetes is also associated with elevated levels of antiangiogenic factors in the third trimester (27). However, the function of placenta in the early stage of pregnancy judged by the level of activin A and inhibin A is often well preserved in diabetic women developing pre-eclampsia (42). Similarly, growth restriction of the fetus is rare in diabetic women with pre-eclampsia (42).

Table 1. Parameters of vascular function at 11 gestational weeks in 83 women with type 1 diabetes in relation to later development of pre-eclampsia

<table>
<thead>
<tr>
<th>Parameter</th>
<th>With Pre-Eclampsia (n=14)</th>
<th>Without Pre-Eclampsia (n=69)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FAD (% of baseline)</td>
<td>107.1±4.9</td>
<td>106.6±5.0</td>
<td>0.77</td>
</tr>
<tr>
<td>NID (% of baseline)</td>
<td>117.2±7.1</td>
<td>122.8±10.1</td>
<td>0.14</td>
</tr>
<tr>
<td>Plasma concentration of VCAM-1 (µg/L)</td>
<td>612±82</td>
<td>516±109</td>
<td>0.003</td>
</tr>
<tr>
<td>Plasma concentration of ICAM-1 (µg/L)</td>
<td>293±67</td>
<td>255±57</td>
<td>0.04</td>
</tr>
<tr>
<td>Plasma concentration of E-selectin (µg/L)</td>
<td>42±20</td>
<td>41±18</td>
<td>0.82</td>
</tr>
<tr>
<td>Plasma concentration of vWf (kIU/L)</td>
<td>1.5 (0.9–2.9)</td>
<td>1.2 (0.6–3.1)</td>
<td>0.11</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.2 (5.9–10.5)</td>
<td>7.2 (5.3–10.9)</td>
<td>0.01</td>
</tr>
<tr>
<td>UAE, (mg/24 h)</td>
<td>194 (3–1104)</td>
<td>7 (0–412)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Systolic BP, (mmHg)</td>
<td>122±12</td>
<td>111±11</td>
<td>0.003</td>
</tr>
<tr>
<td>Diastolic BP, (mmHg)</td>
<td>75±6</td>
<td>69±9</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD or median (range). Adapted from reference 28. FAD, endothelium-dependent flow-associated dilation; NID, nitroglycerin-induced dilation; VCAM-1, vascular cell adhesion molecule 1; ICAM-1, intracellular adhesion molecule 1; HbA1c, hemoglobin A1c; UAE, urinary albumin excretion; vWf, von Willebrand factor.

Pathogenesis of Pre-Eclampsia in Women with Diabetes

We suggest that the increased prevalence of pre-eclampsia in women with type 1 diabetes complicated with diabetic nephropathy or microalbuminuria is mainly related to maternal constitutional factors with an increased susceptibility to endothelial activation (28), whereas poor placentation is not a major pathogenetic factor (42). The pathogenesis of development of pre-eclampsia in women with diabetic nephropathy or microalbuminuria and type 1 diabetes does thus include presence of endothelial dysfunction (28), impaired maximal vasodilation (28), increased levels of prorenin a component of the RAS (36), and markers of cardiac overload (41). All of these can be modulated by antihypertensive treatment. The therapeutic implications of these observations are unknown and require further study.

Prepregnancy Counseling for Women with Diabetic Nephropathy Counseling

Careful counseling of the woman and her partner of the risk for herself and the newborn is important before the couple can make a well considered decision regarding pregnancy. Serum creatinine >176 µmol/L is the best predictor of the risk of pregnancy-induced decline in maternal kidney function leading to ESRD during pregnancy or shortly afterward (23).
In addition, an updated diabetes status, including self-monitored glucose values, HbA1c, risk of severe hypoglycemia, degree of diabetic retinopathy, serum creatinine, BP, and proteinuria, is necessary to estimate the risk for complications during pregnancy in a woman with diabetic nephropathy. In addition to the level of BP per se, the number of antihypertensive agents to control the BP sufficiently before pregnancy is also of importance, because there needs to be room for further intensification of antihypertensive treatment in late pregnancy, if necessary.

Glycemic Control
Poor glycemic control before pregnancy is associated with pregnancy complications such as congenital malformations (43,44), pre-eclampsia (45–47), and preterm delivery (1,43). Strict glycemic control is therefore the goal and HbA1c as close to normal as possible at least <7% is recommended. The risk of severe hypoglycemia has to be taken into account (48).

Low-Dose Aspirin
Low-dose aspirin treatment might prevent pre-eclampsia (49) and can be continued in women already receiving this treatment before pregnancy or initiated after organogenesis.

BP Control
Prepregnancy treatment with ACE inhibitors combined with strict metabolic control for at least 6 months resulting in low levels of albumin excretion has been found to be associated with a high rate of successful pregnancy outcome (4). In this study ACE inhibition was discontinued immediately after the positive pregnancy test and only 4 of 24 women delivered preterm. Severe disability or late intrauterine death was seen in two patients (4).

Intensive glycemic control, low-dose aspirin, and intensive antihypertensive treatment are of importance before pregnancy in women with diabetic nephropathy or microalbuminuria. Blockers of the RAS and statins are contraindicated during organogenesis, but termination of pregnancy is generally not recommended if these drugs are given. Screening for diabetic retinopathy and laser treatment, if indicated, is important.

Cholesterol-Lowering Drugs
Treatment with statins or other cholesterol-lowering drugs during pregnancy may be associated with malformations or changes in the development of the central nervous system and should be discontinued before pregnancy (55).

Diabetic Retinopathy
Laser treatment for diabetic retinopathy should be performed to stabilize the retinopathy before pregnancy, when requested.

Summary of Prepregnancy Care
Intensive glycemic control, low-dose aspirin, and intensive antihypertensive treatment are of importance before pregnancy in women with diabetic nephropathy or microalbuminuria. Blockers of the RAS and statins are contraindicated during organogenesis, but termination of pregnancy is generally not recommended if these drugs are given. Screening for diabetic retinopathy and laser treatment, if indicated, is important.
nephropathy if office BP exceeded 140/90 mmHg or albumin excretion exceeded 2000 mg/24 h. If the women were already taking antihypertensive treatment, the drugs were changed to antihypertensive agents well tolerated in pregnancy such as methyldopa, labetalol, or nifedipine.

In an unselected cohort of 20 normotensive pregnant women with type 1 diabetes and microalbuminuria treated with this strategy, a significant reduction in preterm delivery before 34 gestational weeks was seen compared with a previous cohort in which antihypertensive treatment for elevated BP was less rigorous (54). However, the prevalence of pre-eclampsia and preterm delivery was still high and therefore we decided in 2004 to intensify the strategy by initiating antihypertensive treatment when BP exceeds 135/85 mmHg or urinary albumin excretion exceeds 300 mg/24 h. This strategy seems to be associated with further improvement because fewer women with type 1 diabetes and microalbuminuria developed pre-eclampsia or delivered preterm in a recent recording (Table 2) (2).

Furthermore, early onset and intensive antihypertensive treatment in women with type 1 diabetes and diabetic nephropathy may reduce the severity of pre-eclampsia and preterm delivery (2). It is often necessary to use a combination of different pregnancy-friendly antihypertensive agents to control BP and albumin excretion. Methyldopa, β-blockers (labetalol), and calcium antagonists (nifedipine and diltiazem) are often used and are apparently safe (54,59) in pregnancy. In addition, diuretics, both thiazides and loop diuretics, may be used with caution during pregnancy and we often find it necessary to continue with an unchanged dose of diuretics if the women are already treated with this class of drug before pregnancy due to diabetic nephropathy (54). Many women with diabetic nephropathy can be controlled with one or two antihypertensive agents, but as many as four different antihypertensive classes of drugs, including diuretics, are used for selected pregnant women at our center in order to stabilize the BP (2,54). Although antihypertensive agents have been reported to be associated with intrauterine growth restriction (60), this seemed not to be the case in women with type 1 diabetes and diabetic nephropathy or microalbuminuria (2). Likewise, no cases of stillbirth were observed in the 10 women with microalbuminuria given early and intensive antihypertensive treatment (Table 2) or in the seven women with diabetic nephropathy (2).

Carr et al. (5) described a cohort of 43 pregnant women with diabetic nephropathy in which suboptimal control of hypertension in early pregnancy was associated with increased risk of preterm delivery compared with women with well controlled BP on medical treatment (38% versus 5%).

Although prospective, randomized trials are not available, studies from our center (2,54), in combination with studies

| Table 2. Comparison of pregnancy outcomes in studies of pregnant type 1 diabetic women with microalbuminuria covering the same geographical area in Eastern Denmark |
|-------------------------------------------------|------------------------------|------------------------------|------------------------------|
| Antihypertensive Therapy Strategy               | Ekbom et al., 2001 (25)     | Nielsen et al., 2006 (54)    | Nielsen et al., 2009 (2)     |
|                                                 | Pre-Eclampsia                | BP >140/90 mmHg              | BP >135/85 mmHg              |
|                                                 | Diastolic BP                | UAE >2 g/24 h                | UAE >300/24 h                |
|                                                 | >95 mmHg                    | ACE Inhibitor before Pregnancy | ACE Inhibitor before Pregnancy |
| Number                                          | 26                          | 20                           | 10                           |
| Duration of diabetes (yr)                       | 19±5                        | 18±8                         | 15±10                        |
| HbA1c at inclusion (%)                          | 8.1±0.9                     | 6.8±0.5                     | 7.3±1.5                     |
| Week of onset of antihypertensive therapy       | 29 (20–34)                  | 13 (Before-34)              | 5 (50)                      |
| Patients on antihypertensive therapy during pregnancy | 9 (35)                | 10 (50)                     | Before (Before-14)            |
| ACE inhibitor before pregnancy                  | 5 (19)                      | 9 (45)                      | 4 (40)                      |
| Systolic BP at inclusion (mmHg)                  | 121±13                      | 121±14                      | 117±14                      |
| Diastolic BP at inclusion (mmHg)                 | 71±8                        | 73±8                        | 74±8                        |
| UAE (mg/24 h)                                   | 69 (16–278)                 | 74 (30–287)                 | 91 (30–198)                 |
| Pre-eclampsia                                   | 11 (42)                     | 4 (20)                      | 0                           |
| Preterm delivery before 34 wk                   | 6 (23)                      | 0                           | 0                           |
| Preterm delivery before 37 wk                   | 16 (62)                     | 8 (40)                      | 2 (20)                      |
| Birth weight (g)                                | 3124±767                    | 3279±663                    | 3471±670                    |
| Perinatal mortality                             | 1 (4)                       | 0                           | 0                           |
| Major congenital malformations                  | 1 (4)                       | 0                           | 0                           |

Data are given as mean ± SD, median (range), or n (%). Duration of diabetes, HbA1c, BP, and birth weight in this study are given as mean ± SD to compare results with previous studies from our center (25,54). Slightly modified from reference 2. UAE, urinary albumin excretion; ACE, angiotensin converting enzyme.
by Kimmerle et al. (8) and Carr et al. (5), strongly suggest that women with type 1 diabetes and diabetic nephropathy or microalbuminuria receiving early and intensive antihypertensive treatment have a better pregnancy outcome compared with women initiating antihypertensive treatment in late pregnancy (2).

The mechanism of the effect of early and intensive antihypertensive treatment in pregnant women with microalbuminuria is not known. Antihypertensive treatment may stabilize the urinary albumin excretion and the universal leakage of albumin from the microcirculation and thus improves the endothelial function. The antihypertensive treatment thereby reduces not only BP and urinary albumin excretion but also the other clinical manifestations of pre-eclampsia associated with maternal endothelial dysfunction. The beneficial effect of antihypertensive treatment of microalbuminuria in normotensive patients with type 1 diabetes outside pregnancy is well documented (13).

To detect a possible deterioration of kidney function during pregnancy in women with diabetic nephropathy, measurements of serum creatinine approximately are recommended based on the risk of the individual women; once per month can often be recommended.

Obstetric Surveillance
In late pregnancy, close obstetrical surveillance is important to diagnose complications, prevent stillbirths, and plan the time of delivery. In addition to clinical control, including BP and protein excretion, ultrasound evaluations are performed in order to detect possible growth restriction. In late pregnancy cardiotocography is often performed once or twice weekly in order to detect cardiac morbidity and prevent stillbirth. On special indications, measurements of the flow profile in the umbilical artery or the uterine artery may be added. If pre-eclampsia is suspected measurement of serum urate, serum creatinine and thrombocyte counting is needed. When pre-eclampsia has developed, it is often wise not to postpone the delivery of the fetus. Maturation of fetal lung function with glucocorticoid treatment before preterm delivery before 34 gestational weeks is also recommended in diabetic women.

Diabetic Retinopathy
In addition to protecting kidney function, focus on diabetic retinopathy is important in these women because progression to severe diabetic retinopathy is prevalent during pregnancy (61,62). Notably, higher BP and diabetic nephropathy in early pregnancy may be associated with progression to sight-threatening diabetic retinopathy (62). Laser treatment should be performed during pregnancy, if indicated (62).

Summary of Treatment Recommendations
In summary, strict glycemic control (HbA1c <6.0%), low-dose aspirin, and intensive antihypertensive treatment with pregnancy-friendly drugs are of importance during pregnancy in women with diabetic nephropathy. The goal for antihypertensive treatment includes both BP <135/85 mmHg and urinary albumin excretion <300 mg/24 h and is stricter compared with other pregnant women. Close obstetric surveillance and screening for diabetic retinopathy is important to improve pregnancy outcomes in these high-risk pregnancies.

Future Research
Randomized clinical trials investigating the most appropriate goal for antihypertensive treatment and the type of drugs to use in women with microalbuminuria or diabetic nephropathy are needed. Obstetricians are generally reluctant to lower BP with antihypertensive drugs in late pregnancy. More research on the possible side effects of using antihypertensive drugs in obtaining stringent goals for BP in pregnancy is therefore necessary. Many of the antihypertensive drugs used in pregnancy are obsolete outside of pregnancy and research with currently used antihypertensive drugs is needed.

Pregnancy outcome in women with diabetic nephropathy has improved considerably over the last decade with a take-home-baby rate of approximately 95%. Most information in the literature comes from women with type 1 diabetes and diabetic nephropathy, but the same numbers are probably also valid for women with type 2 diabetes. Careful counseling of women with diabetic nephropathy before pregnancy with estimation of the risk for the mother and fetus is important. Pregnancy does not result in worsening of kidney function in women with diabetic nephropathy and normal serum creatinine, but pregnancy complications are common.

Strict metabolic control before and during pregnancy, low-dose aspirin from 12 gestational weeks and intensive antihypertensive treatment with pregnancy-friendly drugs are important for pregnancy outcomes. Methyldopa, labetalol, and nifedpine are regarded safe in pregnancy whereas ACE inhibitors, AngII antagonists, or statins should not be used during pregnancy. Case series and pathophysiological studies support the use of a stringent goal for BP and albumin excretion in pregnant women with diabetic nephropathy. Screening for diabetic retinopathy before and during pregnancy is mandatory and laser treatment should be performed if indicated. Further research on the benefits and risks of intensive antihypertensive treatment in this population is needed.

Disclosures
None

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