Pregnancy Outcome and its Relationship to Progression of Renal Failure in Autosomal Dominant Polycystic Kidney Disease

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(J. Am. Soc. Nephrol. 1994; 5:1178–1185)

ABSTRACT
The effect of pregnancy on renal disease has not been defined in autosomal dominant polycystic kidney disease (ADPKD). Therefore, fetal and maternal complication rates in ADPKD women as compared with those in unaffected family members (NADPKD) were assessed. Two hundred thirty-five ADPKD and 108 NADPKD women with 605 and 244 pregnancies, respectively, were studied. Overall, fetal complication rates were similar between ADPKD and NADPKD women (32.6 versus 26.2%). Fetal complications were more common in ADPKD women when they were older than 30 yr. Increased fetal prematurity rates were found in preeclamptic ADPKD women as compared with normotensive ADPKD women (28 versus 10%; P < 0.01). More maternal complications occurred in ADPKD as compared with NADPKD women (35 versus 19%; P < 0.001), with preexisting hypertension being the most important risk factor for a maternal complication to occur. Normotensive ADPKD women who developed preeclampsia were more likely to develop chronic hypertension than those without preeclampsia (89 versus 58%; P < 0.01). Hypertensive ADPKD women with four or more pregnancies had lower creatinine clearances than age-adjusted hypertensive ADPKD women with fewer than four pregnancies (49 ± 5 versus 66 ± 3 mL/min per 1.73 m²; P < 0.01). Therefore, normotensive ADPKD women usually have successful, uncomplicated pregnancies. However, hypertensive ADPKD women are at high risk for fetal and maternal complications and measures should be taken to prevent the development of preeclampsia in these women.

Key Words: Preeclampsia, hypertension, renal function, fertility, fetal complications

The relationship between pregnancy and loss of renal function in women with renal disease is not clear (1–6), nor has the effect of preexisting renal disease on fetal outcome been well described (3). In general, pregnancies that occurred before 1970 in women with renal disease demonstrated poorer obstetrical and renal outcome as compared with those occurring in the present day because of less access to medical care, less advanced technology for fetal surveillance, and the limited availability of antihypertensive medications in the past. Similarly, early case reports of autosomal dominant polycystic kidney disease (ADPKD) women who underwent pregnancy demonstrated poor fetal outcome associated with a rapid deterioration in renal function (7–10).

Milutinovic et al. have demonstrated an increased rate of pregnancy-induced hypertension in ADPKD women as compared with unaffected family members (11). More recently, in a longitudinal study, Gabow et al. demonstrated that pregnancy had a negative effect on renal function in women with three or more pregnancies (12). However, the factors responsible for the more aggressive renal course in these women were not identified. In addition, there is a paucity of data regarding fetal outcome in ADPKD women.

In a variety of renal diseases, preexisting renal insufficiency, hypertension, advanced maternal age, and pathologic markers of increased disease activity in inflammatory glomerulopathies have been shown to be risk factors for poor fetal and maternal outcome (13–19). Conversely, women with a renal diagnosis before pregnancy demonstrated better fetal and maternal outcomes as compared with those only diagnosed during or after pregnancy, possibly because of increased maternal surveillance (19–22).

To evaluate these and other potential variables affecting pregnancy outcome in ADPKD, this study examined maternal and fetal complication rates during pregnancy in ADPKD as compared with those in unaffected women in ADPKD families (NADPKD). In addition, the effects of pregnancy number on renal
structure and long-term renal outcome were examined in ADPKD women.

METHODS

Three hundred forty-three ADPKD and NADPKD women from 169 ADPKD families were studied at the General Clinical Research Center at the University of Colorado Health Sciences Center and the Pediatric Clinical Research Center at Children's Hospital (CRC) between June 1985 and June 1993. After giving informed written consent, subjects underwent a complete history and physical examination, including a comprehensive obstetrical history questionnaire (Table 1). Women who were pregnant at the time of evaluation were excluded with reference to the evaluation of renal volume and renal function. At the time of the subject’s visit to the CRC, urine and blood collections, history and physical examinations, and renal ultrasonography were performed.

Fertility rates were determined in both men and women on the basis of the number of conceptions per patient. Nonviable fetuses were classified as spontaneous abortion (spontaneous loss of viability before 20 wk), therapeutic abortion, or elective abortion with therapeutic abortion performed because of health risks to the mother. Stillborn was considered a spontaneous loss of viability after 20-wk gestation. Data were used from pregnancies extending past 20 wk with regard to maternal complication rates and the effects of pregnancy number on renal function and structural involvement, given that renal hemodynamic changes reach a maximum by the middle of the second trimester (23).

Fetal complications of live births were classified as prematurity or term birth with clinical problems. Prematurity was defined as small for dates (intrauterine growth retardation) or premature delivery (delivery before 37-wk gestation). Clinical problems included congenital defects of the cardiovascular, gastrointestinal, or musculoskeletal system, as well as noncongenital medical problems. Perinatal mortality rates were calculated from the number of stillbirths and deaths occurring within the first month of life.

Maternal complications included new-onset or worsening hypertension during pregnancy requiring increased antihypertensive medication to maintain blood pressure control. Chronic hypertension was defined as a blood pressure greater than 140/90 mm Hg or blood pressure requiring antihypertensive medication in the nonpregnant state. Pre-eclampsia was a clinical diagnosis of new or worsening edema with new or worsening hypertension and proteinuria. These findings were confirmed when possible with the treating physician. The presence of proteinuria in ADPKD patients is significant, given that only 18% of the general ADPKD population demonstrate more than 300 mg of urinary protein excretion daily and normotensive ADPKD women with normal renal function have not demonstrated detectable proteinuria (24). When a clear differentiation between hypertension and pre-eclampsia could not be made, women were classified as having new or worsening hypertension during pregnancy. Eclampsia was defined as pre-eclampsia in the setting of grand mal seizures.

The effects of preexisting hypertension, maternal age, the year of pregnancy, and a previous diagnosis of ADPKD on maternal and fetal outcomes were assessed. The year of pregnancy was separated to before or after 1972 because this year marked the legalization of abortion.

A complete abdominal ultrasonogram was performed on all subjects with a high-resolution real-time scanner (Acuson or ATL with a 35- or 5-mm Hz transducer) and a conventional static scanner (Picker 802) as described elsewhere (25). Only studies in the nonpregnant state were included for analysis. Mean renal volume was calculated from both kidneys by use of the following formula for a modified ellipse: \( \frac{4}{3} \pi \left( \frac{\text{length}}{2} \right) \left( \frac{\text{anterior-posterior diameter}}{4} + \frac{\text{width}}{4} \right) \). Mean renal volumes were corrected for body surface area. A patient was diagnosed with ADPKD if more than five cysts were present bilaterally by ultrasonography (26).

Two consecutive 24-h urine collections were obtained for urinary creatinine excretion determinations. A blood sample was obtained in the morning with the patient in the fasting state for the measurement of serum creatinine concentration. Creatinine clearances were calculated and corrected for body surface area. Subjects whose 24-h creatinine excretion rates had a coefficient of variation of more than 15% from the mean and differed by more than 300 mg/day were excluded from the analysis of renal function. Serum and urine creatinine concentrations were determined by the modified Jaffe reaction with the Beckman 2 autoanalyzer.

Comparisons of dichotomous variables between groups were performed by the use of \( \chi^2 \) analysis. Continuous variables were evaluated by the use of a t test. Logistic regression, multiple regression analysis, or analysis of covariance determined the relative importance of more than one variable on fetal and maternal outcome. Mean data are presented with the standard error. Significance was placed at \( P < 0.05 \), and \( P \) values are provided throughout the text.

RESULTS

Two hundred thirty-five ADPKD women with 605 pregnancies and 108 NADPKD women with 244 pregnancies were available for study. Ninety-one women (62 ADPKD and 29 NADPKD) were not included in the analysis of creatinine clearance because of current pregnancy status \((N = 5)\), creatinine excretion variability \((N = 33)\), different laboratory source for creatinine data \((N = 17)\), or missing data \((N = 36)\). Seven as compared with 4% of ADPKD and NADPKD pregnancies were delivered by cesarean section \((P = \text{not significant} [\text{NS}])\). Mean time from last pregnancy to CRC visit was 15 ± 1.0 and 17 ± 1.4 yr in ADPKD and NADPKD women respectively \((P = \text{NS})\). Sixty-nine and 75% of ADPKD and NADPKD women, respectively,
were studied 5 or more years after their last pregnancy. The mean age (42 ± 1 [ADPKD] versus 40 ± 1 [NADPKD] yr), the number of pregnancies (2.6 ± 0.1 [ADPKD] versus 2.3 ± 0.2 [NADPKD]), and the percentage of women with a history of pregnancy (80 [ADPKD] versus 75% [NADPKD]) were not different between groups. One hundred fifty-nine ADPKD and 90 NADPKD men of similar age responsible for 283 and 150 pregnancies, respectively, were studied. The fertility rates of ADPKD and NADPKD men were similar (1.8 ± 0.1 versus 1.8 ± 0.2; P = NS).

Four hundred sixty-eight (77%) of 605 and 200 (82%) of 244 pregnancies in ADPKD and NADPKD women, respectively, resulted in a live birth (P = NS). The number of spontaneous, therapeutic, and elective abortions as well as stillbirths in both groups are provided in Table 2. Six percent as compared with 15% of spontaneous abortions occurred in the second trimester in ADPKD and NADPKD women, respectively (P = NS). There were seven ectopic pregnancies in ADPKD women compared with one ectopic pregnancy in the NADPKD group, which, although not statistically different, is noteworthy. The ectopic pregnancy was the only therapeutic abortion in the NADPKD group. There were 12 therapeutic abortions in the ADPKD group—7 for ectopic pregnancies, 2 for early worsening maternal hypertension, 1 for severe fetal polycystic kidney disease and marked oligohydramnios, 1 after maternal exposure to German measles, and 1 for unclear reasons. Therefore, 10 of 12 therapeutic abortions were potentially performed for reasons directly related to ADPKD. The frequency of therapeutic abortions did not differ before or after 1972 in either ADPKD or NADPKD patients (ADPKD women, 1 versus 3%; P = NS). Fifty-five percent of ADPKD and 64% of NADPKD pregnancies occurred before 1972, with elective abortions occurring in 0.3% of pregnancies before and 12% of pregnancies after 1972 in ADPKD women and 0% before and 7% after 1972 in NADPKD women.

The effects of maternal age, year of pregnancy, previous diagnosis of ADPKD, and previous diagnosis of hypertension on the number of live births (excluding elective abortions) are shown in Figure 1A. When pregnancies resulting in elective abortions are excluded, only the presence of hypertension affected the number of pregnancies resulting in a live birth in

<p>| Table 2. Classification of nonviable fetuses in ADPKD and NADPKD women |
|--------------------------|--------------------------|--------------------------|--------------------------|</p>
<table>
<thead>
<tr>
<th>Classification</th>
<th>ADPKD (N, %)</th>
<th>NADPKD (N, %)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancies</td>
<td>605 (1%)</td>
<td>244 (1%)</td>
<td>NS</td>
</tr>
<tr>
<td>Nonviable Fetuses</td>
<td>137 (23%)</td>
<td>44 (18%)</td>
<td>NS</td>
</tr>
<tr>
<td>Spontaneous Abortion</td>
<td>72 (12%)</td>
<td>44 (13%)</td>
<td>NS</td>
</tr>
<tr>
<td>Therapeutic Abortion</td>
<td>12 (2%)</td>
<td>1 (0.4%)</td>
<td>NS</td>
</tr>
<tr>
<td>Elective Abortion</td>
<td>36 (6%)</td>
<td>7 (3%)</td>
<td>NS</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>17 (3%)</td>
<td>5 (2%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Figure 1. (A) The effects of maternal age, year of pregnancy, previous diagnosis of ADPKD, and previous diagnosis of hypertension on the percentage of live births, excluding elective abortions (DX, diagnosis; HBP, high blood pressure). (B) The effects of maternal age, year of pregnancy, previous diagnosis of ADPKD, and previous diagnosis of hypertension on fetal complications in live births. (C) The effects of maternal age, year of pregnancy, previous diagnosis of ADPKD, and previous diagnosis of hypertension on maternal complications in pregnancies extending past 20 wk.

ADPKD women (hypertensive versus normotensive, 73 versus 83%; P = 0.06). Logistic regression analysis of the above-mentioned variables demonstrated that only the presence of preexisting hypertension was
independently related to the successful outcome of a pregnancy \( (P = 0.06) \).

Four hundred eight (67%) ADPKD as compared with 180 (74%) NADPKD live births were without fetal complications \( (P = NS; \text{ Table 3}) \). Increased maternal age and year of pregnancy affected the rate of occurrence of fetal complications in ADPKD and NADPKD women (Figure 1B). Logistic regression also demonstrated that only these two variables significantly and independently affected fetal complications in live births in ADPKD women. When women with multiple pregnancies were considered, 42 (27%) of 153 ADPKD women as compared with 11 (16%) of 69 NADPKD women had fetal complications in more than one pregnancy \( (P = 0.06) \). Overall, fetal prematurity occurred in 9% of 485 ADPKD pregnancies, with an overall perinatal mortality rate of 4.1% (Table 4). Normotensive ADPKD and NADPKD women had similar perinatal mortality rates (3.4 versus 2.4%; \( P = NS \)). Normotensive ADPKD women demonstrated significantly lower prematurity rates than all preeclamptic ADPKD women \( (P < 0.01) \). When hypertensive or preeclamptic ADPKD women were compared with normotensive ADPKD women, the perinatal mortality rate tended to be greater, but was not statistically different \( (P = 0.07) \).

ADPKD women developed maternal complications more frequently than NADPKD women (35 versus 19%; \( P < 0.001 \)) (Table 5). New or worsening hypertension, preeclampsia, and edema occurred more frequently in ADPKD as compared with NADPKD women. Preeclampsia occurred in 54 ADPKD pregnancies, in which 20 were nulliparous and 34 were multiparous. The frequency of other complications did not differ between ADPKD and NADPKD women; however, 9 of 24 other complications in ADPKD women were directly related to the presence of ADPKD. Four of these nine complications (0.8% of all ADPKD pregnancies) were acute renal failure in the setting of hypertension, preeclampsia, and placenta abruptio, whereas a fifth patient developed placenta abruptio in the setting of hypertension. Acute renal failure occurred as recently as 1986 in two cases. Only one of the four women has entered ESRD, age 41 yr, 12 yr after the episode of acute renal failure. No case of acute renal failure was reported in NADPKD women. Three ADPKD patients developed a renal cyst infection or acute symptoms of nephrolithiasis, and one patient had severe peripartum hemorrhage in the setting of preeclampsia, requiring multiple blood transfusions. Uncomplicated urinary tract infections were reported in five as compared with four pregnancies in ADPKD and NADPKD women, respectively.

ADPKD women with a complication in their first pregnancy were older than ADPKD women with uncomplicated first pregnancies (24.3 ± 0.6 versus 22.8 ± 0.4 yr; \( P < 0.05 \)). More maternal complications occurred in ADPKD women if the pregnancy occurred after 1972, if maternal age was more than 30 yr, if a

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**TABLE 3. Frequency and type of fetal complications in live births**

<table>
<thead>
<tr>
<th>Complications</th>
<th>ADPKD N (%)</th>
<th>NADPKD N (%)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Live Births</td>
<td>468 (13)</td>
<td>200</td>
<td>NS</td>
</tr>
<tr>
<td>Any Fetal</td>
<td>60 (13)</td>
<td>20 (10)</td>
<td>NS</td>
</tr>
</tbody>
</table>
| Intrauterine Growth
   Retardation | 7 (1.5)     | 2 (1)        | NS            |
| Premature     | 28 (6)      | 8 (4)        | NS            |
| Premature with Clinical Problems | 9 (2) | 8 (4) | NS |
| Term with Clinical Problems | 11 (2) | 2 (1) | NS |
| Birth Defects\( a \) | 0 (0)     | 0 (0)        | NS            |
| Other         | 5 (1)       | 0 (0)        | NS            |

\( a \) Two premature infants (and three nonviable fetuses) were also noted as having birth defects.

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**TABLE 4. Prematurity and perinatal mortality rates in NADPKD, normotensive, and hypertensive ADPKD women with and without preeclampsia**

<table>
<thead>
<tr>
<th></th>
<th>ADPKD( a )</th>
<th>NADPKD ( b )</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prematurity N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NADPKD, 205</td>
<td>23 (11)</td>
<td>5 (2.4)</td>
<td></td>
</tr>
<tr>
<td>All ADPKD, 485</td>
<td>59 (12)</td>
<td>20 (4.1)</td>
<td></td>
</tr>
<tr>
<td>NBP ADPKD, No Preeclampsia, 410</td>
<td>40 (10)( b )</td>
<td>14 (3.4)( c )</td>
<td></td>
</tr>
<tr>
<td>HBP ADPKD, No Preeclampsia, 22</td>
<td>4 (18)</td>
<td>1 (4.6)</td>
<td></td>
</tr>
<tr>
<td>NBP ADPKD Preeclampsia, 34</td>
<td>9 (26)</td>
<td>3 (8.8)</td>
<td></td>
</tr>
<tr>
<td>HBP ADPKD Preeclampsia, 19</td>
<td>6 (32)</td>
<td>2 (10.5)</td>
<td></td>
</tr>
</tbody>
</table>

\( a \) NBP, normal blood pressure; HBP, hypertension.

\( b \) \( P < 0.01 \), NBP ADPKD versus either group with preeclampsia.

\( c \) \( P = 0.07 \), NBP ADPKD versus all other ADPKD groups combined.

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**TABLE 5. Frequency and type of maternal complications in pregnancies extending past 20 wk\( a \)**

<table>
<thead>
<tr>
<th>Complication</th>
<th>ADPKD N (%)</th>
<th>NADPKD N (%)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancies Extending Past 20 wk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any Maternal Complication</td>
<td>170 (35)</td>
<td>38 (19)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>New HBP</td>
<td>78 (16)</td>
<td>13 (6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Worse HBP</td>
<td>34 (7)</td>
<td>3 (1)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Edema</td>
<td>119 (25)</td>
<td>30 (15)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>51 (11)</td>
<td>9 (4)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Eclampsia</td>
<td>3 (1)</td>
<td>3 (1)</td>
<td>NS</td>
</tr>
<tr>
<td>Other</td>
<td>24 (5)</td>
<td>11 (5)</td>
<td>NS</td>
</tr>
</tbody>
</table>

\( a \) A pregnancy may be associated with more than one complication.
previous diagnosis of ADPKD was present, or if preexisting hypertension was present (Figure 1C). Logistic regression analysis demonstrated that a prior diagnosis of hypertension \((P < 0.0001)\) and the year of pregnancy \((P < 0.05)\) were independently related to maternal complications in ADPKD women. NADPKD women had more maternal complications after 1972 (28 versus 14%; \(P < 0.05)\) and, in contrast, if they were younger than 30 yr of age (22 versus 3%; \(P < 0.01)\). ADPKD women with a complication in their first pregnancy were more likely to have a complication in a succeeding pregnancy as compared with ADPKD women with an uncomplicated first pregnancy (75 versus 26%; \(P < 0.001)\). This was also true for NADPKD women (62 versus 10%; \(P < 0.001)\).

One hundred fifty-seven of 170 ADPKD women with at least one pregnancy were normotensive at the time of the first pregnancy. Thirteen (8%) of these women developed preeclampsia, a significantly lower occurrence as compared with ADPKD women with preexisting hypertension (7 [54%] of 13; \(P < 0.001)\) versus normotensive). Ten of the 13 normotensive ADPKD women subsequently developed chronic hypertension. Thirteen of the remaining 144 who did not develop preeclampsia in their first pregnancy developed eclampsia or preeclampsia in subsequent pregnancies (9%), all of whom later developed chronic hypertension. Therefore, 23 (88%) of 26 women who developed preeclampsia or eclampsia during a pregnancy subsequently developed chronic hypertension. In comparison, only 81 (62%) of 131 who never developed preeclampsia or eclampsia in pregnancy later developed chronic hypertension \((P < 0.01)\). Subject age at time of visit, number of years since last pregnancy, and total number of pregnancies did not differ between those with or without a preeclamptic complication.

Similarly, 39 of 157 normotensive women developed new-onset hypertension during pregnancy, whereas 118 had no hypertensive complications. Thirty-one (79%) of the 39 went on to develop chronic hypertension as compared with 73 (62%) of the 118 \((P < 0.05)\). Those women who had new-onset hypertension during pregnancy developed chronic hypertension at a mean age of 34 yr, \(5 \pm 2 \text{ yr after their last pregnancy, as compared with women without a hypertensive complication during pregnancy, who became hypertensive at a mean age of 45 yr, 16 \pm 2 \text{ yr after their last pregnancy (}P < 0.05)\).

Only 5 of 428 ADPKD pregnancies with available laboratory data occurred in women with serum creatinine concentrations higher than 1.2 mg/dL before pregnancy. All were associated with a fetal or maternal complication, with four of five resulting in a live birth. Four of five women have subsequently entered ESRD at a mean age of 43 yr, 2 to 10 yr after their last pregnancy (mean, 5 yr). Twelve ADPKD patients had serum creatinine concentration determinations performed within 1 yr before pregnancy and at least 6 months after the pregnancy. Mean serum creatinine concentration was not different prepregnancy and postpregnancy \((1.1 \pm 0.1 \text{ mg/dL before and after). Only two ADPKD women were pregnant at the time of study on the CRC and had serum creatinine concentrations of 0.6 and 0.9 mg/dL.\)

Creatinine clearances were significantly lower in ADPKD women with four or more pregnancies as compared with age-adjusted ADPKD women with fewer than four pregnancies \((P < 0.001)\). Age, the presence of hypertension, and the number of pregnancies all had a negative effect on renal function. When hypertensive and normotensive ADPKD women were studied separately, pregnancy number had an adverse effect on renal function in hypertensive ADPKD women only \((P < 0.01)\). Pregnancy number did not relate to the percentage of age-adjusted women with hypertension.

Twenty-eight (12%) of 235 ADPKD women studied have subsequently entered ESRD. These women entered ESRD 22 \pm 2 \text{ yr after their last pregnancy. The mean age of entry into ESRD was 52 \pm 2 \text{ yr. Pregnancy number did not differ between age-adjusted women who have entered ESRD as compared with those who have not entered ESRD. As well, pregnancy number and percentage of pregnancies with maternal complications were not important variables in determining the age of entry into ESRD. Importantly, all women who have subsequently entered ESRD were hypertensive at the time of study.\)

Mean renal volume was similar in ADPKD women with four or more pregnancies as compared with age-adjusted women with fewer than three pregnancies \((495 \pm 79 \text{ versus } 590 \pm 39 \text{ cm}^3/\text{m}^2)\). Hypertensive ADPKD women had larger renal volumes than their normotensive counterparts; however, neither pregnancy number nor age had an effect on renal volume in these women.
DISCUSSION

The influence of pregnancy on the course of renal disease and the effect of renal disease on the outcome of a pregnancy are important issues in treating and advising patients with renal disease. Despite the relevance of these questions, they remain unanswered for many renal diseases, including ADPKD. In the past, obtaining the answers to these questions was less urgent than it is now because patients were often not diagnosed with ADPKD until they were past childbearing age. However, in our study population, the mean age of diagnosis was 31 yr, and currently, the disease is often diagnosed in childhood (27). This earlier age of diagnosis as well as the presence of ADPKD in more than a quarter of a million women in the United States has provided an impetus to understand the effect and outcome of pregnancy in ADPKD.

The first question of reproductive interest in ADPKD is that of fertility. Given the occurrence of ovarian cysts in ADPKD women (28) and reports of altered sperm motility in ADPKD men (29), a decrease in fertility might have been anticipated. However, in this study, fertility rates in both ADPKD men and women were comparable to those observed in unaffected male and female family members.

The occurrence of seven ectopic pregnancies in ADPKD women compared with one in NADPKD women is noteworthy. Although this was not statistically significant, it may have some clinical relevance. Importantly, Milutinovic et al. also reported two ectopic pregnancies in their ADPKD population as compared with none in the NADPKD population (11). Given the alterations in the epithelia in ductal organs found in ADPKD, it is possible that the oviduct epithelia are also abnormal. Because severe abdominal pain in ADPKD patients is often assumed to be renal in origin, this diagnostic possibility should be kept in mind in ADPKD women of childbearing age.

The second question of reproductive interest in this population is the frequency of elective abortion. Given the hereditary nature of this disease, one might have expected this to be higher in affected subjects compared with unaffected family members. Although the frequency of elective abortion increased in both affected and unaffected women after 1972, with the legalization of abortion, it was not significantly different in ADPKD as compared with NADPKD women. As well, the rate of therapeutic abortions did not change after 1972, suggesting that elective abortions had not been classified as therapeutic abortions before 1972. Importantly, 10 of 12 therapeutic abortions in ADPKD women appear to be directly related to a consequence of ADPKD. The lack of difference between ADPKD and NADPKD women with regard to the occurrence rate of elective abortions is in keeping with the data of Sujan et al., which demonstrated that only 4% of affected adult subjects would have an abortion if the fetus had ADPKD (30). It is also consistent with the low use of gene linkage technology for the prenatal diagnosis of ADPKD (31).

The third question relates to short- and long-term maternal outcome. Sixteen percent of ADPKD women in this study developed new-onset hypertension during pregnancy, similar to rates found in other studies of ADPKD women (11,15). Twenty-five percent developed a hypertensive complication during pregnancy, including new or worsening hypertension, with 11% developing preeclampsia. This is a higher rate than that found by Milutinovic et al., who reported a 3.2% occurrence rate of preeclampsia (11). This difference may be in part because his patient population was approximately 10 yr younger. Although biopsy material is not available to confirm the presence of glomerular endotheiosis in the pregnancies in this study, the lack of detectable proteinuria in normotensive ADPKD women with normal renal function, who comprised the majority of this study population (24), makes the inclusion of proteinuria a valid criterion in differentiating preeclampsia from pregnancy-induced hypertension.

Of interest, normotensive ADPKD women who developed either preeclampsia or hypertension were at greater risk for the development of chronic hypertension as compared with their non-preeclamptic or non-hypertensive counterparts. This suggests that hypertensive complications in pregnancy in ADPKD women predict the future development of chronic hypertension. This is similar to essential hypertension, i.e., women in the general population who had developed transient hypertension in pregnancy were more likely to develop chronic hypertension (32).

It is important to note that four pregnancies (0.8%) resulted in acute renal failure in ADPKD women. Although this is not a common event, it is strikingly more common than the current incidence rate of obstetrical acute renal failure in the general population of 1 in 10,000 (31). Given that all cases of acute renal failure were in the setting of preeclampsia, measures to prevent this from occurring are worthwhile.

Pregnancy number had a mild but significantly negative effect on long-term renal function in hypertensive ADPKD women. This effect was only statistically evident in women with four or more pregnancies. However, in this analysis, pregnancy number did not affect the age of entry into ESRD in ADPKD women; this may be because the number of ADPKD women who have entered ESRD is small (N = 28). Importantly, 80% of women who underwent pregnancy with prepregnancy serum creatinine concentrations of more than 1.2 mg/dl have since entered ESRD at a mean age approximately 15 yr earlier than that of the general female ADPKD population (12). Although the number of patients available for review is extremely small, ADPKD appears to be similar to other renal disorders, in that underlying renal insufficiency before pregnancy may have an adverse effect on long-term renal outcome (34–36).

A direct relationship between renal cystic involve-
ment and pregnancy was not found, suggesting that the hormonal changes that occur during pregnancy do not promote renal cystogenesis. This differs from the relationship found between pregnancy number and liver cystic involvement (37).

The final question, of course, is the outcome of the pregnancy. There were no fetal or maternal complications in the majority of ADPKD women in this study; however, it is important to note that only 5 of 428 ADPKD pregnancies with available data had serum creatinine concentrations of more than 1.2 mg/dL before conception. Because the majority of this study population had normal renal function before conception, it is not surprising that preexisting hypertension demonstrated the most negative effect on maternal and fetal outcome in this study. Prematurity rates were significantly higher in ADPKD women with superimposed preeclampsia as compared with their normotensive counterparts. Although not significant (P = 0.07), perinatal mortality rates tended to increase in those with a hypertensive complication during pregnancy. Both prematurity and perinatal mortality rates in pregnancies complicated by hypertension or preeclampsia were higher than rates reported in mild essential hypertensive women (38,39) and in the general high-risk obstetrical population (40). Given that arteriolar nephrosclerosis is the major, noncystic, renal pathologic finding in ADPKD (41), it is of interest that perinatal mortality and prematurity rates of hypertensive ADPKD women with preeclampsia were similar to those reported in women with biopsy-proven arteriolar nephrosclerosis with moderate or severe hypertension and superimposed preeclampsia (42). This suggests an important role for renal vascular disease in the hypertensive complications in pregnancy.

Although a diagnosis before pregnancy has offered improved fetal and maternal outcomes in other renal disorders, such as focal segmental glomerulosclerosis, immunoglobulin A nephropathy, or membranoproliferative glomerulonephritis (43-45), the positive benefits of a preexisting diagnosis were not found in the ADPKD women in this study. Information is not available concerning the reason for diagnosis in this patient population, but those who carried a diagnosis before pregnancy may have been symptomatic, suggestive of more severe disease.

This large comprehensive study of the maternal and fetal outcomes of pregnancy in ADPKD women provides the basis for the counseling and care of ADPKD women who are considering pregnancy or who are pregnant. In summary, the occurrence of fetal complications in any pregnancy appears to be a marker for fetal complications in future pregnancies. ADPKD women with preeclampsia have higher prematurity and perinatal mortality rates. The development of preeclampsia during pregnancy identifies those women who are at increased risk for developing acute renal failure during pregnancy and who are more likely to develop chronic hypertension. Loss of renal function is associated with increasing pregnancy number in hypertensive ADPKD women. Women with hypertension diagnosed before pregnancy are at risk for increased fetal loss, maternal complications, and the development of preeclampsia. These patients represent a high-risk group worthy of increased surveillance during pregnancy (46). Conversely, normotensive women with previous uncomplicated pregnancies have a good chance of having a successful, uncomplicated pregnancy.

ACKNOWLEDGMENTS

This research was supported by Grant 5 P01 DK34039, Human Polycystic Kidney Disease (PKD), awarded by the Department of Health and Human Services, Public Health Service, NIDDK, and Grant MORR-00051 and R800069 from the General Clinical Research Centers' Research Program of the Division of Research Resources, National Institutes of Health.


