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Peutz-Jeghers syndrome and family planning: the attitude towards prenatal
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Running title: Peutz-Jeghers syndrome and family planning

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26 **ABSTRACT**

27 Peutz-Jeghers syndrome (PJS) is a hereditary disorder caused by *LKB1* gene mutations, and is
28 associated with considerable morbidity and decreased life expectancy. This study was
29 conducted to assess the attitude of PJS patients towards family planning, prenatal diagnosis
30 (PND) and pregnancy termination and preimplantation genetic diagnosis (PGD). In a cross-
31 sectional study, 61 adult PJS patients were asked to complete a questionnaire concerning
32 genetic testing, family planning, PND and PGD. The questionnaire was completed by 52
33 patients (85% response rate, 44% males) with a median age of 45 (range 18-74) years. Thirty-
34 seven (71%) respondents had undergone genetic testing. Twenty-four respondents (46%, 75%
35 males) had children. Fifteen (29%) respondents reported that their diagnosis of PJS had
36 influenced their decisions regarding family planning, including 10 patients (19%, 9/10
37 females) who did not want to have children because of their disease. Termination of
38 pregnancy after PND in case of a foetus with PJS was considered ‘acceptable’ for 15% of the
39 respondents, whereas 52% considered PGD acceptable. In conclusion, the diagnosis of PJS
40 influences the decisions regarding family planning in one third of PJS patients, especially in
41 women. Most patients have a negative attitude towards pregnancy termination after PND,
42 while PGD in case of PJS is judged more acceptable. These results emphasize the importance
43 of discussing aspects regarding family planning with PJS patients, including PND and PGD.

44

45 **Keywords:** Peutz-Jeghers syndrome, family planning, genetic testing, preimplantation
46 genetic diagnosis, prenatal diagnosis.

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50 INTRODUCTION

51 Peutz-Jeghers syndrome (PJS) is a rare, autosomal dominant inherited disorder caused
52 by germline mutations in the *LKB1* gene.¹⁻² The syndrome is clinically characterized by
53 gastrointestinal hamartomas and mucocutaneous pigmentation.³⁻⁴ Hamartomatous polyps can
54 develop already in the first decade of life and may cause various complications, including
55 anaemia, bleeding and acute intestinal obstruction.⁵⁻⁶ Furthermore, PJS is associated with an
56 increased cancer risk in adult life. Lifetime cumulative cancer risks as high as 93% have been
57 described.⁷⁻⁸ These clinical aspects of the disease affect the psychological condition and
58 quality of life of PJS patients. They suffer from mild depression and experience a poorer
59 mental quality of life, more limitations in daily functioning due to emotional problems, and a
60 poorer general health perception compared to the general population.⁹⁻¹⁰

61

62 Performing genetic testing might influence family planning of patients. Diagnostic
63 mutation analysis is available for patients clinically suspected of PJS. If a pathogenic
64 mutation is confirmed, antenatal genetic testing of offspring is available through prenatal
65 diagnosis (PND) (i.e. chorionic villus sampling and amniocentesis), which may result in the
66 wish to terminate the pregnancy in case of an affected foetus. In addition, preimplantation
67 genetic diagnosis (PGD) has become available. PGD involves in vitro fertilization (IVF). One
68 or two cells of a 3-day old embryo created *in vitro* are analysed for the genetic defect, and
69 only embryos with an unaffected genotype are selected for transfer to the uterus.¹¹ Although
70 PND and PGD are available for hereditary cancer syndromes in most European countries, the
71 application of these techniques remains controversial in the social, ethical and political
72 domain.¹²

73

74 Data concerning family planning of patients with PJS are lacking. Therefore, the aim
75 of this study was to investigate the desire to have children in PJS patients, and their attitudes
76 towards PND with the implication of pregnancy termination and towards PGD.

77 **METHODS**

78 **Patients**

79 A total of 61 PJS patients from 39 families from two Dutch academic hospitals were
80 invited to complete a questionnaire on genetic testing, family planning, PND, and PGD. The
81 study was approved by the Institutional Review Boards of both participating hospitals.
82 Patients were eligible if they were aged 18 years or older and fulfilled the diagnostic criteria
83 for PJS recommended by the World Health Organisation (see supplementary information
84 online).¹³ The questionnaire, an information-folder, a consent form and a reply paid envelop
85 were sent to all potential participants by mail. After 6 and 12 weeks a reminder was sent to
86 non-respondents.

88 **Measures**

89 The questionnaire was earlier described in detail by van Lier et al.¹⁰ Briefly, it
90 comprised a range of demographic variables including age, gender, and parenthood. As
91 psychological determinants, concerns regarding cancer were assessed with the cancer worry
92 scale (CWS)¹⁴, and illness perceptions were evaluated by the Illness Perception
93 Questionnaire-Revised (IPQ-R).¹⁵ Clinical variables including history of cancer and family
94 history of PJS were derived from medical records.

95 In addition, respondents were asked whether or not they had undergone genetic testing
96 and, if they had, what the result had been. Self-reported data regarding genetic testing were
97 confirmed by medical records where possible. Questions were posed about the current desire
98 to have (more) children, and if the diagnosis of PJS had influenced the desire to have (more)
99 children. Furthermore, after a short introductory text about PND and PGD, respondents were
100 asked whether or not they considered termination of pregnancy after PND or the use of PGD

acceptable; (1) in general, and (2) in case of PJS (see supplementary information online).

Response categories were ‘yes’, ‘no’ or ‘unsure’.¹⁶

Statistical analysis

Data were analyzed using the SPSS 17.0 statistical software for Windows. Descriptive statistics were used to characterize the study sample. Continuous variables were reported by means (and standard deviation) and medians (and range). Univariate analyses (χ^2 , Fisher’s exact test, independent *t*-test and Mann-Whitney U test) were used to evaluate which sociodemographic, clinical and psychological variables were related to attitudes towards genetic testing, PND and PGD. A two-sided *P*-value < 0.05 was considered statistically significant. Multivariate logistic regression analyses using backward selection with a *P*-value of 0.1 for removal of the variable was carried out to determine associations between possible confounders (sociodemographic, personal and family medical history, and psychosocial determinants) and three outcome measures: genetic testing (‘yes’ or ‘no’), termination of pregnancy after PND acceptable in case of PJS (‘yes’ or ‘no/unsure’) and PGD acceptable in case of PJS (‘yes’ or ‘no/unsure’).

RESULTS

Baseline characteristics

The questionnaire was completed by 52 PJS patients (response rate 85%) from 34 families. Median age of respondents was 44.5 (18-74) years and 23 (44%) were male. Baseline characteristics of the respondents and non-respondents are shown in Table 1.

There were no significant differences in age ($P=0.056$) or cancer incidence between male and female respondents ($P=0.144$). However, women in our cohort scored significantly higher than men on the cancer worry scale (6.41 vs. 5.13, $P=0.038$), and on the IPQ-R subscale *emotional representations* (16.21 vs. 12.87, $P=0.019$). Scores on the other six IPQ-R subscales did not differ significantly between male and female respondents.

Genetic testing

Of the 52 patients who completed the questionnaire, 37 patients had undergone genetic testing, of which 33 (89%) were actually carrier of a pathogenic *LKBI* mutation. Multivariate logistic regression analysis showed female gender ($P=0.035$) and parenthood ($P=0.016$) as positive predictors for genetic test uptake (Supplementary Table 1).

Parenthood and influence of PJS on family planning

Twenty-four respondents (46%; median age 50 years) had children. Female PJS patients less often had children than male patients (25% versus 75%, $P<0.001$).

Fifteen of the 52 respondents (29%, median age 44 years) reported that the diagnosis of PJS had influenced their desire to have children (i.e. less or no children). Ten of these 15 respondents (19%; median age 45 years) stated that they had decided to have no children because of PJS, including 9 females and one male, the latter whom had adopted a child. Cancer incidence was higher in these 10 patients (56% vs. 44%, $P=0.011$), and they scored

144 higher on the cancer worry scale (8.0 vs. 5.2, $P=0.039$) compared to the other respondents.

145 Twenty-three of the respondents (44%, median age 45 years) indicated that PJS had not

146 influenced their desire to have children.

147
148 In general, the majority of respondents considered termination of pregnancy after PND
149 and the use of PGD as ‘acceptable’ (62% and 61%, respectively). The attitude of respondents
150 regarding these two techniques in relation to PJS is shown in Figure 1. Fifteen per cent of
151 patients considered pregnancy termination after PND acceptable, while 52% accepted the use
152 of PGD in case of PJS. Results of univariate and multivariate analyses are shown in Table 2
153 and 3. No significant associations were found for the attitude towards pregnancy termination
154 after PND or towards PGD.

DISCUSSION

This is the first survey among PJS patients that evaluated their decisions regarding family planning, and their attitude towards PND with possible pregnancy termination, and towards PGD. Twenty-four respondents (46%, 75% males) had children. Interestingly, there was a notable gender difference in our study population with respect to parenthood. Female patients less often had children than men with PJS. Furthermore, 90% of patients (9 / 10) who explicitly indicated that they did not want to have children because of PJS were female. The reason for this difference is not clear. As PJS is associated with an increased risk for the development of gynaecological tumours^{8,17}, disabilities (e.g. hysterectomy or oophorectomy) might have prevented female patients from having children. However, this was the case in only 2 females from our cohort (at the age of 36 and 39 years). In addition, there were no significant differences in age or cancer incidence between male and female respondents. One could postulate that psychosocial explanations for this difference exist. Women in our cohort did have more cancer worries than men, and had a higher emotional response to PJS. These findings could imply that women are more emotionally affected by their disease which can render to a higher sense of responsibility towards their offspring.¹⁸

All respondents, irrespective of parenthood or not, were asked about their attitude towards termination of pregnancy after PND. More patients accepted the use of PGD in case of PJS than pregnancy termination after PND, suggesting a preference for PGD. This preference has been observed before in couples with different genetic disorders, including cancer susceptibility syndromes as hereditary breast and ovarian cancer, and familial adenomatous polyposis syndrome.¹⁹⁻²³ In a recent study among 210 couples with a broad spectrum of genetic disorders, the majority of couples preferred PGD over PND for diagnostic testing in a future pregnancy.²⁴ The preference for PGD can partly be explained by the fact that PGD

181 offers patients the possibility to have an unaffected genetically related child while termination
182 of a pregnancy can be avoided. Furthermore, early reassurance is seen as an important
183 advantage.¹⁹ Though, many individuals with a hereditary condition for which PGD has been
184 permitted, are unfamiliar with the technique or even unaware of its existence.²⁴ In practice,
185 PGD is physically and psychologically burdensome.²⁵ Our questionnaire did not explore the
186 knowledge of respondents about PND and PGD. Although both techniques were shortly
187 described, the information might have been too limited. Furthermore, positive attitudes
188 towards PND and PGD do not necessarily translate into actual use.²⁶

189
190 This study is hampered by some limitations. First of all, the cross-sectional study design
191 makes evaluation of causal interactions impossible. Instead, we can only demonstrate
192 statistical associations between determinants and the attitude towards genetic testing and
193 reproductive decision making. Second, only affected individuals were asked to fill in the
194 questionnaire, not their partners, yet it is likely that partners of PJS patients play an important
195 role in the reproductive decision making and family planning. Third, the actual use of PND
196 and subsequent pregnancy termination and PGD amongst PJS patients is not known and
197 questions regarding religion were not included in our questionnaire, while religion can be of
198 influence on the attitude towards both PND as well as PGD. Finally, in spite of the response
199 rate of over 85%, our conclusions are drawn from a small sample size. Since PJS is a rare
200 disorder it is difficult to assess a larger group. However, we managed to approach nearly all
201 known Dutch PJS patients, thereby creating a heterogeneous cohort of patients enrolled in
202 similar surveillance programs and with similar access to medical care. To our knowledge this
203 is the first report concerning reproductive decision making and the attitude towards antenatal
204 diagnostics amongst PJS patients.

In conclusion, this study demonstrates that the diagnosis of PJS influences decisions regarding family planning in approximately one third of PJS patients, especially in women. The majority of patients undergo genetic testing, and many PJS patients have a positive attitude towards PGD as an option to prevent transmission of PJS to their offspring. In contrast, the attitude of respondents was predominantly negative towards pregnancy termination after PND in case of a foetus affected with the syndrome. Our results emphasize not only the importance of accurate genetic counselling for these patients; it also indicates that medical specialists dealing with patients suffering from hereditary cancer syndromes, including PJS, should discuss aspects regarding family planning such as PND and PGD.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Title and legend to figure

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Figure 1. Attitude of PJS patients towards termination of pregnancy after PND and preimplantation genetic diagnosis in case of PJS.

Legend:

PND: Acceptance of termination of pregnancy after PND in case of PJS.

PGD: Acceptance of the use of preimplantation genetic diagnosis in case of PJS.

Table 1 Baseline characteristics of respondents and non-respondents.

| | Respondents | Non-respondents |
|----------------------------------|--------------|-----------------|
| | N (%) | N (%) |
| | 52 | 9 |
| Median age (range)* | 44.5 (18-74) | 34 (18-67) |
| ≤ 45 yrs (childbearing age) | 29 (55.8) | 5 (55.6) |
| > 45 yrs | 23 (44.2) | 4 (44.4) |
| Gender* | | |
| Male | 23 (44.2) | 6 (66.7) |
| Female | 29 (55.8) | 3 (33.3) |
| Partner | | |
| Yes | 36 (69.2) | Unknown |
| No | 16 (30.8) | Unknown |
| Children | | |
| Yes | 24 (46.2) | 5 (55.6) |
| No | 28 (53.8) | 4 (44.4) |
| Educational level | | |
| Low | 29 (55.8) | Unknown |
| High | 23 (44.2) | Unknown |
| Genetic testing performed | | |
| Yes | 37 (71.2) | 9 (100) |
| No | 15 (28.8) | 0 (0) |
| Family history | | |
| Familial PJS | 33 (63) | 5 (55.6) |
| Sporadic PJS / Family unknown | 19 (37) | 4 (44.4) |

338 **Age ($P=0.86$) and gender distribution ($P=0.29$) did not differ between respondents and non-*
339 *respondents.*

Table 2 Determinants of the attitude towards termination of pregnancy in case of a foetus with PJS (N=51)

| | Univariate analysis | | Multivariate logistic regression analysis | |
|-----------------------------------|-------------------------|---------|---|---------|
| | OR (95% CI) | P value | OR (95% CI) | P value |
| Gender; male/female | 2.609 (0.472;14.406) | 0.271 | - | |
| Age | 0.936 (0.877;0.998) | 0.042 | - | |
| Aware of mutation status; yes/no* | 0.680 (0.149;3.099) | 0.618 | | |
| Children; yes/no | 0.124 (0.014;1.098) | 0.061 | - | |
| PJS familial; yes/no | 0.655 (0.133;3.218) | 0.602 | | |
| Malignancy; yes/no | 0.625 (0.067;5.822) | 0.680 | | |
| CWS score | 1.165 (0.881;1.540) | 0.283 | | |

Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval; CWS, cancer worry scale.

* Twenty-nine respondents were aware of their mutation status; 27 LKBI mutation positive and 2 LKBI mutation negative.

Table 3 Determinants of the attitude towards preimplantation genetic diagnosis in case of PJS (N=47)

| | Univariate analysis | | Multivariate logistic regression analysis | |
|-----------------------------------|------------------------|---------|---|---------|
| | OR (95% CI) | P value | OR (95% CI) | P value |
| Gender; male/female | 1.455 (0.454;4.664) | 0.529 | - | |
| Age | 1.021 (0.978;1.067) | 0.341 | - | |
| Aware of mutation status; yes/no* | 1.700 (0.525;5.500) | 0.376 | | |
| Children; yes/no | 1.135 (0.356;3.621) | 0.831 | | |
| PJS familial; yes/no | 0.343 (0.078;1.500) | 0.155 | | |
| Malignancy; yes/no | 0.375 (0.078;1.803) | 0.221 | | |
| CWS score | 1.187 (0.884;1.593) | 0.254 | | |

Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval; CWS, cancer worry scale.

* Twenty-nine respondents were aware of their mutation status; 27 LKBI mutation positive and 2 LKBI mutation negative.

SUPPLEMENTARY INFORMATION

Diagnostic criteria for Peutz-Jeghers syndrome (PJS) recommended by the WHO

A. Positive family history of PJS, and

1. Any number of histologically confirmed PJS polyps, or

2. Characteristic, prominent, mucocutaneous pigmentation.

B. Negative family history of PJS, and

1. Three or more histologically confirmed PJS polyps, or

2. Any number of histologically confirmed PJS polyps and characteristic,
prominent, mucocutaneous pigmentation.

SUPPLEMENTARY INFORMATION

Questionnaire concerning prenatal diagnosis and preimplantation genetic diagnosis

Prenatal diagnosis

With prenatal diagnosis it is possible to test the unborn child for the genetic defect causing PJS during pregnancy. When the child is a carrier of this genetic defect, selective termination of pregnancy (abortion) can be considered.

1. For a pregnancy of *someone I know*, termination of pregnancy is unacceptable in every situation.

Yes / no / don't know

2. *For me*, termination of pregnancy is acceptable if the (unborn) child is a carrier of the genetic defect for Peutz-Jeghers syndrome

Yes / no / don't know

Preimplantation genetic diagnosis

Preimplantation genetic diagnosis (PGD) is a new technique, not yet available for everyone. PGD is done after in vitro fertilization (IVF). A genetic defect can be detected 3 days after fertilization of an egg. Only those embryos which do not have the genetic defect are put back into the womb of the woman to mature the pregnancy. We are interested in your opinion about this new technique.

1. For a pregnancy of *someone I know*, PGD is unacceptable in every situation.

Yes / no / don't know

2. *For me*, the use of PGD is acceptable, because the (unborn) child could be a carrier of the genetic defect causing Peutz-Jeghers syndrome.

Yes / no / don't know

388 **Supplementary Table 1 Determinants of genetic testing (N=52)**

| | Univariate analysis | | Multivariate logistic regression analysis | |
|----------------------|----------------------------|----------------|--|----------------|
| | OR (95% CI) | <i>P</i> value | OR (95% CI) | <i>P</i> value |
| Gender; male/female | 1.676 (0.501;5.611) | 0.402 | 11.344 (1.183;108.805) | 0.035 |
| Age | 1.042 (0.995;1.092) | 0.080 | - | |
| Children; yes/no | 3.235 (0.869;12.043) | 0.080 | 17.664 (1.726;180.818) | 0.016 |
| PJS familial; yes/no | 1.333 (0.357;4.985) | 0.669 | | |
| Malignancy; yes/no | 1.517 (0.277;8.310) | 0.631 | | |
| CWS score | 0.962 (0.750;1.235) | 0.763 | | |

389 Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval; CWS, cancer worry scale.

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