Should we vaccinate against and test for human papillomavirus infection in adolescent girls and women with a neovagina?

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INTRODUCTION

Complex anomalies of the reproductive and genital tract occur in 1 in 2000–3000 women resulting in approximately 25 000 affected women in the UK (Table 1).1–4 These conditions include disorders of sex development such as androgen insensitivity syndrome (AIS) and congenital adrenal hyperplasia, anomalies of the Müllerian system such as the Mayer-Rokitansky-Küster-Hauser syndrome (MRKH) where the vagina and uterus are absent, and various other abnormalities of development of the genital tract where menstruation is blocked.

Management of these women is complex and should be led by a multidisciplinary team with input from gynaecologists, urologists, colorectal surgeons, endocrinologists, geneticists, nurse specialists, radiologists, biochemists and psychologists. Patients should feel comfortable and empowered enough in the multidisciplinary team setting to contribute to making decisions regarding their own health care. The aims of management should be to achieve optimal physical and psychological health with good quality of life, sexual function and fertility options. To achieve this, it is often necessary to create a vagina for these women—a so-called ‘neovagina’.5

The National Health Service (NHS) Cervical Screening Programme screens over 3 million women each year to detect and treat precancerous cervical abnormalities. However, it is accepted that cervical smears are not useful in screening women with a neovagina unless a cervix is present, and most women with these conditions are advised to opt out of the national screening programme. In practical terms it is not possible to do a smear if no cervix is present. In addition, smears taken from the neovagina vary depending on the tissue used to line it and are difficult for cytolgists to interpret. However the recent introduction of vaccination and testing for human papillomavirus (HPV) may be appropriate for women with a neovagina and this needs further evaluation to allow clinicians to advise women appropriately.

Many of the patient support groups for women with complex congenital anomalies are very active and include relevant peer-reviewed literature on their websites. This commentary was prompted by our experience of how patient education via a support group was able to empower one young woman to question our practice (Box 1). The aim of this commentary is to review the literature and to report our findings as well as the outcomes and

Table 1 Complex anomalies of the reproductive and genital tract

<table>
<thead>
<tr>
<th>Condition</th>
<th>Incidence</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mayer-Rokitansky-Küster-Hauser syndrome</td>
<td>1 in 5000</td>
<td>Attomaki et al.1</td>
</tr>
<tr>
<td>Congenital adrenal hyperplasia</td>
<td>1 in 30 000 females</td>
<td>Pang et al.2</td>
</tr>
<tr>
<td>Complete androgen insensitivity syndrome</td>
<td>1 in 40 000</td>
<td>Boehmner et al.3</td>
</tr>
<tr>
<td>Turner syndrome</td>
<td>1 in 3000</td>
<td>Gravholt et al.4</td>
</tr>
<tr>
<td>Complex Müllerian anomalies (transverse septa, obstructed hemivagina, etc.)</td>
<td>~1 in 5000</td>
<td>No recent medical literature</td>
</tr>
</tbody>
</table>
The gynaecology team was contacted for advice by a 26-year-old woman with Rokitansky syndrome (absent vagina and cervix) who had undergone formation of a neovagina by vaginal dilatation. She had accessed a paper from the medical journal *Fertility and Sterility* via a patient support group website reporting vaginal intraepithelial neoplasia and adenocarcinoma in women with a neovagina.12

This prompted our literature review, which was presented as a poster at two conferences and generated much debate. The patient took a copy of the poster to her appointment with her general practitioner’s (GP’s) practice nurse to request vaccination against human papillomavirus (HPV).

Despite this, the GP is unhappy to provide the HPV vaccination but has offered an appointment to discuss the ‘no need’ to vaccinate with her. We have written to the GP to explain our concerns.

Booking the appointment, attending and asking for what she wanted was difficult for our patient.

barriers we have encountered. We also make recommendations for current clinical practice and further research.

**CREATION AND MANAGEMENT OF A NEOVAGINA**

Creation of a neovagina can be achieved via a non-surgical or a surgical approach depending on the diagnosis, previous treatment and patient preference. Variations in surgical approach and timing of operations exist, with some women having had surgery in infancy and others in adolescence or adulthood. In adolescent and adult women, non-surgical treatment is achieved by a course of vaginal dilatation. Dilatation of the vaginal dimple has become more commonplace as primary treatment within the last decade and is the first choice of treatment for women with a shortened or absent vagina and no previous surgical reconstruction.

If dilatation is unsuccessful or not indicated, then a variety of surgical techniques exist. The laparoscopic Vecchietti procedure is increasingly performed and involves the use of a traction device to stretch the vaginal dimple. Dilatation and the Vecchietti procedure have the benefit of creating a neovagina lined with tissue very similar to normal vaginal epithelium.6 There also exist a wide range of alternative surgical approaches where the neovagina is lined with a variety of tissues including skin grafts, rotational skin flaps, peritoneum (the Davidoff procedure), or created with segments of bowel, usually a portion of sigmoid colon maintaining its blood supply from the inferior mesenteric artery. Any woman undergoing creation of a neovagina is encouraged to attend for review and follow-up with in a specialist service as longer-term complications can occur.

However, women often disengage from hospital follow-up around the time of transition from paediatric care to adult services and then struggle to re-engage. They may not wish to attend their primary care provider because they feel their conditions are not understood7 despite their general practitioner being well placed to support their long-term health needs. Sexual health and family planning staff can also have an important role in the care of these women if sexual health has not been addressed adequately in paediatric services.8 9 We recognise that these complex conditions can be quite daunting to manage, even for tertiary medical staff, but professionals need to be mindful that these women can be disenfranchised and subject to stigma and shame so deserve to be treated with compassion and empathy.

**HUMAN PAPILLOMAVIRUS**

Sexually active women are at risk of acquiring HPV infections. There are at least 100 types of HPV. Certain types – so-called ‘high-risk’ – are associated with cervical cancer and are found in over 99% of cervical cancers.10 This has led to a national HPV vaccination programme for adolescent girls in the UK. Many of our complex patients do not have a cervix and therefore assume, or are told, that they do not need to be vaccinated against HPV.

Within the NHS, HPV triage for low-grade smears and ‘test of cure’ smears after treatment for cervical intraepithelial neoplasia (CIN) 2 and 3 have now been introduced nationwide. In the future, women may have a high-risk HPV test first and only ever get a cervical smear if they test positive for high-risk HPV types associated with cervical cancer. If women with a neovagina are not attending for cervical screening, then they will not be offered HPV testing.

**LITERATURE REVIEW**

A review of the literature was undertaken. Medline was searched through PubMed using the following MeSH terms: AIS, CAIS (complete androgen insensitivity syndrome), MRKH syndrome, vaginal intraepithelial neoplasia (VAIN), vaginal cancer/neoplasms, vulvar cancer/neoplasms, papillomavirus vaccines and HPV. The patient, intervention, comparison and outcome (PICO) structure was used to build the search.

Only eight relevant papers were identified. In women with a native (normal) vagina, there is evidence that HPV infection is associated with genital warts, vaginal, vulval and anal intraepithelial neoplasia (VAIN, VIN and AIN) and vaginal, vulval and anal cancers as well as CIN and cervical cancer.11
To date, there have been no published papers on HPV vaccination or testing in women with, or likely to need, a neovagina. However, HPV infection, genital warts, VAIN, VIN and vaginal cancer have all been found in women with a neovagina.\textsuperscript{12} The first symptoms of cancer of the neovagina are a clear or bloody discharge and postcoital bleeding. Cancer of the neovagina occurs at a younger age than cancer of the native vagina.\textsuperscript{13} Adenocarcinomas occur in vaginas made of bowel and squamous carcinomas occur in vaginas made of skin grafts or flaps.\textsuperscript{14} Neovaginal tissues are subject to stresses that they are not accustomed to such as vaginal dilatation, sexual intercourse and semen and it has been suggested that these stresses may result in the neoplastic changes found at a younger age in this group of patients.\textsuperscript{14} This also makes it difficult for histopathologists to assess the tissues for pathology.

The Vecchietti procedure and vaginal dilatation both result in a vagina composed of tissue very similar to normal vaginal epithelium.\textsuperscript{6} This may be advantageous in relation to HPV infection. Native-type tissue in the vagina may be less likely to undergo neoplastic change in relation to functions such as sex, dilatation and exposure to semen. One study examined vaginal smear tests from patients who had had a Vecchietti procedure between 2 and 12 years previously.\textsuperscript{15} Whilst the authors observed HPV infections, no neoplastic lesions were found.

**CLINICAL IMPLICATIONS**

**HPV testing**

HPV testing can be performed in a neovagina, meaning that these women could be included in a future initial phase of population testing. There is no current evidence to guide management of high-risk HPV positive women with a neovagina. However, given the associated risks identified in the literature review, best practice could be vaginoscopy with 5% acetic acid in a colposcopy clinic with facilities for biopsy, with ablation or excision by a colposcopist with experience of complex congenital anomalies of the genital tract and the issues arising from HPV infection in women with a neovagina. The frequency of and the upper age limit for follow-up is unknown. Follow-up should therefore be done as part of a prospective research study.

**Vaccination**

It would seem sensible, however, to vaccinate in order to prevent HPV infection in the first place, considering the potentially serious sequelae and our lack of knowledge about management of high-risk HPV-positive patients with a neovagina. Vaccination with the quadrivalent HPV vaccine would also prevent genital warts in this population, which can be a problem and which are more complicated to treat than in the general population. We recognise that HPV vaccine uptake can be variable and further study is needed across all populations.\textsuperscript{16}

**CONCLUSION AND CLINICAL RECOMMENDATIONS**

This review has demonstrated the lack of available information on HPV and the neovagina for clinicians and affected women. However, given the fact that HPV has been demonstrated in the neovagina, we recommend that all adolescent girls are offered vaccination. HPV testing in women with a neovagina is unevaluated and given the rarity of their conditions, it is unlikely that large studies will ever be performed. However, it would seem logical to test for HPV at the same time intervals as in the NHS Cervical Screening Programme.

In addition, this commentary illustrates the importance of dialogue with patients, particularly when they have complex or rare medical conditions. There are times when any of us as medical professionals can be faced with a patient who has a complex condition we are unsure about. The patient is likely to know more about their condition than we do, which is understandable considering their vested interest as a sufferer. We hope that providing patients with evidence about what they need does not threaten medical colleagues: rather it helps them to provide the best possible care.

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