Terminology for cone dimensions after local conservative treatment for cervical intraepithelial neoplasia and early invasive cervical cancer: 2022 consensus recommendations from ESGO, EFC, IFCPC, and ESP

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Local cervical treatment for squamous intraepithelial lesion (SIL) or cervical intraepithelial neoplasia (CIN) removes or ablates a cone-shaped or dome-shaped part of the cervix that contains abnormal cells. This Series paper introduces the 2022 terminology for cone dimensions after local conservative treatment for SIL, CIN, or early invasive cervical cancer. The terminology was prepared by the Nomenclature Committee of the European Society of Gynaecologic Oncology, the European Federation for Colposcopy, the International Federation of Cervical Pathology and Colposcopy, and the European Society of Pathology. Cone length should be tailored to the type of transformation zone. Treatment of SIL or CIN is associated with an increased risk of preterm birth, which escalates with increasing cone length. There is a lack of agreement regarding terms used to report excised specimen dimensions both intraoperatively and in the pathology laboratory. Consensus is needed to make studies addressing effectiveness and safety of SIL or CIN treatment comparable, and to facilitate their use to improve accuracy of antenatal surveillance and management. This Series paper summarises the current terminology through a review of existing literature, describes new terminology as agreed by a group of experts from international societies in the field of cervical cancer prevention and treatment, and recommends use of the new terminology that will facilitate communication between clinicians and foster more specific treatment guidelines that balance obstetrical harm against therapeutic effectiveness.

Introduction

Cervical cancer can be prevented by local treatment of screen-detected precursors, such as high-grade squamous intraepithelial lesions—also known as cervical intraepithelial neoplasia (CIN) of grade 2 or worse (CIN2+).1-3 In England, almost 5 million women are invited for cervical cancer screening and more than 33 000 cervical high-grade abnormalities are diagnosed each year,4 although this figure is expected to substantially reduce with the advent of vaccination.5

Local cervical treatment for squamous intraepithelial lesion (SIL) or CIN removes or ablates a cone-shaped or dome-shaped part of the cervix that contains abnormal cells. Nowadays, excisional treatments are preferred over ablation6 because they permit histological exploration of excised tissue to rule out invasion and assess for the presence of residual disease at the excision margins. Large loop excision of the transformation zone (LLETZ), also known as loop electrosurgical excisional procedure, is the treatment of choice in most European countries because of the ease and speed of execution, rapid learning curve, and low cost (figure 1). However, preferred treatment varies throughout Europe and globally, with some countries regularly offering cold knife conisation (CKC), laser conisation, needle excision of the transformation zone, or types of ablation.7

Complications of surgical conservative treatments were thought to be relatively mild and infrequent and were historically described as primary or secondary haemorrhage, infection, and cervical stenosis. However, evidence published in the past 15 years has also associated these procedures with increased reproductive morbidity in women who become pregnant after treatment.8-10 The extent of the risk of reproductive morbidity appears to be directly correlated to the dimensions of the cone removed.11-15 The length of the excised specimen (cone) is commonly used to inform women about their individual risk, and to make antenatal surveillance and interventions more accurate and effective in subsequent pregnancies. Cone length has also been correlated with disease recurrence rates (eg, the smaller the cone, the higher the recurrence rate).16-19 Although the size of the excised specimen is widely used by gynaecologists and pathologists to counsel women and assess treatment, there is a lack of consensus regarding the nomenclature describing dimensions of excised specimens and principles of reporting before and after formalin fixation. Different terminology has been adopted by various gynaecological and pathological societies, with little interaction between the two groups. In this Series paper, we synthesise existing literature about historically used terminology by gynaecological societies in the clinic at the time of treatment, and by pathological societies in the histopathology laboratory. We discuss how the dimensions of excised specimens could be used to assist clinical decision making, and Institute of Reproductive and Developmental Biology, Department of Metabolism, Digestion, and Reproduction (Prof M Kyrgiou PhD, A Athanasiou MBBS[Eq); Department of Surgery and Cancer, Imperial College London, London, UK (Prof M Kyrgiou, A Athanasiou); Imperial College Healthcare NHS Trust, London, UK (Prof M Kyrgiou, A Athanasiou); Prof E Paraskevaidis PhD); Unit of Cancer Epidemiology, Belgian Cancer Centre, Sciensano, Brussels, Belgium (Prof M Arbyn PhD); Department of Human Structure and Repair, Faculty of Medicine and Health Sciences, Ghent University, Ghent, Belgium (Prof M Arbyn); Department of Pathology, Hospital Graz II, Medical University of Graz, Graz, Austria (Prof S F Lax PhD); School of Medicine, Johannes Kepler University Linz, Linz, Austria (Prof S F Lax); Histopathology and Molecular Diagnostics, Careggi University Hospital, Florence, Italy (M R Raspolli [PhD); Department of Obstetrics and Gynaecology, Helsinki University Central Hospital, Helsinki, Finland (P Nieminen PhD); Department of Obstetrics and Gynaecology, Hôpital Nord, APHM, Aix Marseille University, Marseille, France (Prof FX Carcopino PhD); Department of Obstetrics and Gynaecology, Galilee Medical Center, Nahariya, Israel (Prof J Bornstein MD); Department of Obstetrics and

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Figure 1: Local excision of the transformation zone
Adapted with permission from Jo’s Cervical Cancer Trust.†† LLETZ=large loop excision of the transformation zone.

present joint nomenclature from the European Society of Gynaecological Oncology (ESGO), the European Federation for Colposcopy (EFC), the International Federation of Cervical Pathology and Colposcopy (IFCPC), and the European Society of Pathology (ESP) for the description of these dimensions to be used in clinical reporting. Assessment of such reporting to date is hampered by the use of different terms across studies.

Oncological outcomes
Local treatment for SIL or CIN is highly efficacious in preventing cervical cancer and high-grade preinvasive lesion recurrence. Arbyn and colleagues reported an average risk of histologically confirmed high-grade lesion recurrence of only 6-6% following treatment. Although a Cochrane review reported no evidence of a difference in risk of lesion recurrence between surgical techniques, this review only included small randomised controlled studies, so was underpowered to show significant differences between highly efficacious methods of treatment. Emerging data suggest that length and radicality of treatment might affect that risk. In the meta-analysis by Arbyn and colleagues, LLETZ had a 6-7% risk of high-grade SIL or CIN recurrence, whereas CKC and laser conisation only had a 2.1-2.2% risk of recurrence. Additionally, Strander and colleagues reported a gradual increase in age-standardised incidence of invasive cervicovaginal cancer after excisional treatment over the span of five decades, which could partly be explained by the increasing use of less radical surgical techniques. Further research combining observational and randomised evidence is expected to clarify the efficacy of various treatments.

There is a small amount of evidence regarding the association between lesion recurrence rates and the dimensions of excised specimens. Bae and colleagues in a 2013 Korean retrospective cohort study of 1220 women (289 women [24%] CIN grade 2 [CIN2], 916 women [75%] CIN grade 3 [CIN3], and 15 women [1%] stage 1a1 cervical cancer), suggested that cone length should be adjusted according to the age and grade of a lesion (<40 years and CIN2: ≥9 mm; 40–50 years and CIN2: ≥12 mm; ≤50 years and CIN3 or stage 1a1 cervical cancer: ≥18 mm). A cone length of at least 18 mm would be required to achieve resection of a clear endocervical margin in 86% of women younger than 50 years with CIN2+ and in 88% of women younger than 40 years with CIN2+. For CIN2, a 9 mm cone length achieved clearance in 83% of women younger than 50 years, whereas a cone length of 12 mm would be required to achieve clearance in 90% of women younger than 50 years. An observational study by Ang and colleagues of 1558 treated women (482 [31%] CIN2, 1076 [69%] CIN3) found a significantly higher rate of involved endocervical margins in excised specimens measuring less than 10 mm in length than in larger excised specimens in both younger and older women (≤35 years, <10 mm vs ≥10 mm: 24% vs 13%, p=0.001; >35 years, <10 mm vs ≥10 mm: 41% vs 26%, p=0.008). However, the study reported that the difference in rates of margin clearance between specimen lengths led to an increased risk of CIN2+ recurrence for women older than 35 years (but not in younger women). Although margin status is associated with treatment failure, other evidence suggests that human papillomavirus (HPV) clearance is a better predictor of disease outcomes. No studies have explored the effect of cone length on lesion recurrence rates for glandular disease alone.

Reproductive outcomes
Local SIL or CIN treatment has been reported to increase the risk of adverse reproductive outcomes in subsequent pregnancies. In the UK, 2-5% of total preterm births each year (840 preterm births, including 196 with gestational age of <32 weeks) were attributed to previous treatment for SIL or CIN. The first meta-analysis to recognise this association was published in 2006. It reported an increased risk of preterm birth, defined as birth at fewer than 37 weeks’ gestation, after CKC (14%) versus no treatment (5%; relative risk 2.59, 95% CI 1.80–3.72) and LLETZ (11%) versus no treatment (7%.
A subsequent meta-analysis of 20 studies was the first to report that the frequency and severity of reproductive complications increased when surgical treatment methods that are known to remove large amounts of cervical tissue were used. Although SIL or CIN treatment has not been found to affect pregnancy rates, it has been associated with an increased risk of second-trimester miscarriage.\textsuperscript{32,33}

An update to Kyrgiou and colleagues\textsuperscript{10} was published in 2016 and was the first meta-analysis to report that excised specimen length, dimensions, and volume can stratify the rate of reproductive risk.\textsuperscript{11} This meta-analysis reported a relative increase in risk of preterm birth for women after any local treatment compared with no treatment of 1.54 (95% CI 1.09–2.18) for excised specimen lengths up to 10 mm, 1.93 (1.62–2.31) for those measuring 10–15 mm, 2.77 (1.95–3.93) for those measuring 15–20 mm, and 4.91 (2.06–11.68) for those measuring more than 20 mm. The meta-analysis also reported that having SIL or CIN conferred an increased risk of preterm birth, but local treatment increased this risk even further. The additional risk of preterm birth conferred by cones of less than 10 mm in length remains unclear. Noehr and colleagues\textsuperscript{31} reported a 6% increase in risk of preterm birth for every additional millimetre of excised specimen length measuring more than 20 mm. The meta-analysis also concluded that excised specimen volumes of more than 2.65 cm\textsuperscript{3} doubled the risk of preterm birth compared with excised specimen volumes of less than 2.65 cm\textsuperscript{3}.\textsuperscript{12} Khalid and colleagues\textsuperscript{16} reported that risk of preterm birth increased by 150% when cone length exceeded 20 mm (compared with <10 mm), and increased by 300% when excised specimen volume was greater than 6 cm\textsuperscript{3} (compared with <3 cm\textsuperscript{3}).\textsuperscript{13}

Proportional length or volume of cervix removed might be a stronger predictor of poor reproductive outcomes than absolute length or volume of cervix removed, as pretreatment dimensions of a cervix can vary substantially.\textsuperscript{14–17} Research in network meta-analyses\textsuperscript{15,16,18} provided further evidence regarding how cone dimensions or treatment technique affect risk of recurrence or preterm birth.

\textbf{Previous terminology}

\textbf{In the clinic or operating theatre}

The practice of excised specimen measurement before formalin fixation has emerged since the awareness that local SIL or CIN treatment increases the risk of preterm birth in subsequent pregnancies. It has been proposed that excised specimen measurement taken at the time of treatment prior to formalin fixation might be more accurate than excised specimen measurement taken in the histopathology laboratory after formalin fixation.\textsuperscript{19} Cone size has been suggested as a useful measurement for risk stratification that could predict individualised risk of obstetrical complications and make antenatal surveillance and preventive interventions more accurate and effective. Historically, different metrics have been used to describe the dimensions of excised tissue specimens, although these metrics are not universally accepted.

\textbf{Cone dimensions}

The IFCPC attempted to standardise terminology for cone dimensions by publishing guidelines in 2012.\textsuperscript{20} The terminology in these guidelines is the same as the terminology published by Khalid and colleagues\textsuperscript{16} in 2012 (appendix pp 2–3, 5). The IFCPC recognised a lack of consensus in published literature regarding the terms used to describe cone dimensions. For example, the distance from the ectocervical margin to the endocervical margin has been variably reported as length, depth, or height in different publications. As a result, the IFCPC advised abandoning the terms depth and height, and proposed using the term length instead. Furthermore, they introduced the terms thickness and circumference to describe other relevant cone dimensions. However, despite their introduction, these terms have not been largely adopted in clinical practice because of challenges in measuring these dimensions and a lack of guidance regarding how these new terms can affect clinical decision making. Given the asymmetry of excision cones, for example, use of the term thickness (radius) varies in the four quadrants of a cone, and anteroposterior and transverse dimensions are suggested to be more representative of their true size.

\textbf{Cone volume}

Several approaches have been proposed for the measurement of cone volume. The volumetric fluid displacement technique is likely to represent the most accurate measurement (the gold standard), whereby the difference in fluid level before and after the immersion of a cone is recorded (Archimedes’ principle; appendix p 6).\textsuperscript{33,34} When this technique is not feasible, researchers have used various formulas to calculate the volume of a cone from its dimensions.\textsuperscript{33,34–36} As the shape of cones can vary, researchers have used different cone shapes to determine volume, such as a cone, a semi-ellipsoid, an ellipsoid, a parallelepiped, and a truncated cone (frustum; appendix pp 2–3, 7–8).

\textbf{Cervical dimensions}

Cervical dimensions (anteroposterior dimension, transverse dimension, and length) have historically been
Proposed terminology for measurement of the dimensions and volume of the cone and cervix

<table>
<thead>
<tr>
<th>Definition</th>
<th>Cone dimensions</th>
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<tbody>
<tr>
<td></td>
<td>Length: Distance between the ectocervical (external or distal) and endocervical</td>
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<td></td>
<td>(internal or proximal) margin of the cone</td>
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<td></td>
<td>Anteroposterior dimension: Distance between the anterior and posterior margin of</td>
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<td>the cone; if the cone is not oriented, the anteroposterior dimension should be</td>
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<td>randomly selected</td>
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<td>Transverse dimension: Distance between the left and right margin of the cone;</td>
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<td></td>
<td>if the cone is not oriented, the transverse dimension should be randomly selected</td>
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<th>Cone volume</th>
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<tr>
<td>Fluid displacement technique: Volumetric tube</td>
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<tr>
<td>Formula: Semi-ellipsoid: volume = (π/6) × anteroposterior dimension ×</td>
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<td>transverse dimension × length</td>
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<th>Cervical dimensions</th>
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<tr>
<td>Length: Distance between the ectocervical (external or distal) and endocervi</td>
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<td>(internal or proximal) margin, if this distance is measured by ultrasonogra</td>
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<td>phy it should be done with an empty bladder and without applying pressure on</td>
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<td>the cervix</td>
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<tr>
<td>Anteroposterior dimension: Distance between the anterior and posterior aspect</td>
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<td>of the cervical canal in the sagittal view</td>
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<tr>
<td>Transverse dimension: Distance from side to side in the transverse view in</td>
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<td>the midcervix</td>
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<th>Cervical volume</th>
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<td>Three-dimensional transvaginal ultrasonography: Three-dimensional volumetric</td>
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<td>software</td>
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<tr>
<td>Formula: Cylinder: volume = n × ((anteroposterior dimension × transverse</td>
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<tr>
<td>dimension)² × length</td>
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**Figure 2: Proposed terminology for cone dimensions**

Length is the distance of endocervical canal between the ectocervical (external or distal) and the endocervical (internal or proximal) margins. The presence or absence of preinvasive disease in both ectocervical and endocervical margins should be recorded. If margins are clear, a measurement of the distance (in mm) between the preinvasive cells and the closest resection margin can be provided, but this depends on local practice and is optional. This distance should always be recorded in the presence of invasive disease. Based on data from Public Health England and the Royal College of Pathologists.

The 2022 statement by ESGO, EFC, IFCPC, and ESP recommends the adoption of new terminology (table, figure 2). This new terminology should be applied to all measurements of cones in both treatment centres and histopathology laboratories, as well as to measurements of the cervix by imaging. The statement was prepared following teleconferences, a compilation of comments by

measured with transvaginal ultrasonography or MRI of the pelvis (appendix pp 2–3, 9). Cervical length with ultrasonography was defined as the distance from the external os to the internal os with an empty bladder and without applying pressure. Cervical length with MRI was also defined as the distance from the external os to the internal os. In both imaging modalities, the anteroposterior dimension was defined as the distance between the anterior margin and posterior margin of the cervix and the transverse dimension was defined as the distance between the left margin and the right margin of the cervix.

**Cervical volume**

In transvaginal ultrasonography, some researchers used advanced three dimensional (3D) volume calculation software to calculate cervical volume, whereas other researchers used formulas based on cervical dimensions to calculate cervical volume. In MRI, researchers used the volume formula for cylinders to calculate cervical volume (appendix pp 2–3, 9).

**In the histopathological laboratory**

The terms used in histopathological laboratories have been reported by several scientific societies and textbooks, but there are inconsistencies. The term depth was used in histopathological laboratories, as well as to measurements of the cervix by imaging. The statement was prepared following teleconferences, a compilation of comments by

2022 ESGO, EFC, IFCPC, and ESP terminology

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each society, and an expert review. Discrepancies were resolved through discussion and a consensus was reached.

Cone dimensions and volume

The term length should be used to describe the distance of the endocervical canal between the ectocervical (external or distal) and endocervical (internal or proximal) margins. The ruler should be placed perpendicular to the external (distal) cone base. The terms depth, thickness, and height should be abandoned and replaced by the term length. The term anteroposterior dimension should be used to describe the distance between the anterior margin and posterior margin of the cone. If the cone is not oriented, the anteroposterior dimension should be randomly selected and reported. The terms longitudinal, diameter, thickness, and radius should be abandoned and replaced by the term anteroposterior dimension. A suture at the top of the cone should be used for orientation if possible, but this approach is optional. The term transverse dimension should be used to describe the distance between the left margin and the right margin of the cone. If the cone is not oriented, the transverse dimension should be randomly selected and reported. The terms width, thickness, and side-to-side diameter should be abandoned and be replaced by the term transverse dimension.

All three dimensions should be measured and reported (in mm) in the following order: anteroposterior dimension, transverse dimension, then length. For top hat excision (eg, additional excision of endocervical tissue after the main excision of the transformation zone), all three dimensions should be reported for both excisions. The lengths of the two excision specimens should be added together and the total length should also be recorded. For piecemeal excisions, in which the transformation zone is removed through additional peripheral excision or excisions after the main excision, dimensions of all fragments should be recorded, but lengths should not be added together. Only the length of the main central fragment should be used to predict the risk of preterm birth in subsequent pregnancies. Castanon and colleagues reported that the largest length of piecemeal excisions is correlated with a similar risk of preterm birth to the risk in women who have a single-piece excision of the same length.

Measurement of the dimensions of the base of the cone (distal at ectocervix) is compulsory. Other dimensions and the dimensions of the top of the cone (proximal at endocervix) can be recorded for research purposes but are optional. Additional dimensions that can be reported include the circumference of the top and base of the cone and the lateral length (which represents the lateral dimension between the lateral ectocervical and endocervical margin). When the dimensions of both the base and top of the cone are reported, subscript B and T should be used to define the different measurements (appendix p 10).

Separate measurements before and after formalin fixation are not required but should be taken before tissue processing. Fixation in the usual concentration of 10% formalin (or 4% formaldehyde) leads to shrinkage of the sample of 0–3% (at 25°C shrinkage is 3% and at 37°C it is negligible). On the contrary, subsequent tissue processing can lead to shrinkage of up to 20%, depending on the temperature during fixation and the quality of fixation. For example, insufficient duration of fixation might lead to greater shrinkage during tissue processing.

This guidance supports the practice that, ideally, cervical measurements should be taken by both colposcopists and pathologists. Measurements taken by colposcopists are optional but represent best practice and should be recorded in the procedure notes and on the pathology request form. Discrepancies should be assessed in future research. Measurements by colposcopists should be used in preference to pathology measurements for future risk assessment, if available. Measurements taken at time of treatment might not always be possible to obtain and are only encouraged when time restraints and clinical capacity allow. If colposcopy measurements are unable to be obtained, pathology measurements should be taken instead. Measurements taken by colposcopists are useful for several reasons. They permit direct assessment of a cone at the time of excision by the operating colposcopist, which improves measurement accuracy. The measurements can also facilitate future research or inform the need for potential further excision at time of treatment. UK clinical guidelines have recommended different lengths of excision according to the type of transformation zone (appendix p 11). Type 1 transformation zone requires an excision of 7–10 mm in length, type 2 transformation zone requires an excision of 10–15 mm in length, and type 3 transformation zone requires an excision of 15–25 mm in length. Thickness (according to the previous IFPC terminology) of less than 2.9 mm is suggested to increase the risk of involved stromal margin. Furthermore, the knowledge and documentation of cone dimensions in the clinic by the colposcopist can inform counselling and antenatal management in subsequent pregnancies.

Measurement of cone volume is optional and currently considered experimental. The volume value should be recorded, if available, for research purposes and not for clinical use. Further research is required to explore how cone volume correlates to clinical outcomes and how it compares with cone length as a predictor of all outcomes. The fluid displacement technique should be used for measurement. If this technique is not feasible, cone volume should be calculated using the volume formula for a semi-ellipsoid (table). Although volume formulas for several shapes have previously been used to measure cone volume, including the cone, the parallelepiped, and the frustum (truncated cone), the semi-ellipsoid is a more accurate depiction of the true curvature of the proximal side of the cone. Furthermore, the
semi-ellipsoid calculation only requires three dimensions that are measured routinely (anteroposterior dimension, transverse dimension, and length). Different formulas can be used based on clinical judgement if different cone shapes are present (appendix pp 7–8).

**Cervical dimensions and volume**

New proposed terminology (anteroposterior dimension, transverse dimension, and length) should be used in ultrasonography or MRI for the description of cervical dimensions. In ultrasonography, 3D volumetry should be used to calculate cervical volume. If 3D volumetry is not available, cervical volume can be calculated from the cervical dimensions using the cylinder formula (table). Measurements of cervical dimensions and volume of the whole cervix are optional and currently considered experimental. These measurements should be recorded, if available, for research purposes and not for clinical use. Further research is required to explore how the proportion of removed cervical length or volume correlates to clinical outcomes.

**Discussion and clinical use**

The 2022 statement by ESGO, EFC, IFCPC, and ESP recommends the introduction of and universal use of a single set of terminology in both the clinic and the histopathology laboratory that can facilitate more accurate and effective communication of results, clinical decision making, and patient counselling. This terminology will improve recording of results, future research, and meta-analyses.

The rigorous reporting of dimensions should be available for effective patient counselling at colposcopy clinics and antenatal clinics. The majority of women undergoing treatment for SIL or CIN are younger than 40 years, so the introduction of standardised terminology could assist in making antenatal management and interventions more effective when trying to prevent reproductive complications, stratified to individual risk. The knowledge that SIL or CIN treatment increases the risk of preterm birth has led to major changes in clinical practice, not only in colposcopy but also in antenatal care. Many obstetrical units have introduced cervical length measurement for women with history of conisation and, if necessary, preventive treatments such as cervical cerclage, progesterone, and antenatal corticosteroid therapy are given. However, practices across obstetrical units vary and are resource-dependent, unit-dependent, and clinician-dependent. In some clinical settings, cervical length measurement for women with history of conisation has become the standard of care without strong evidence of its benefit. In other clinical settings, only women with either cone length more than 10 mm or repeat conisations are offered antenatal interventions.

The accurate prospective recording of cone and cervix dimensions will permit further research to stratify women by risk of poor reproductive outcomes antenatally and offer risk-limiting interventions to those most at risk, particularly in limited-resource settings. Furthermore, measurement of dimensions of either cones or cervixes at treatment centres and clinics could further improve treatment quality and margin clearance. Existing colposcopy databases should be adapted to routinely document the proposed dimensions and volumes and collect prospective long-term data on both oncological outcomes and reproductive outcomes. Increasing cone length at local treatment has been previously associated with reduced risk of lesion recurrence and higher rates of preterm birth. Data from prospective databases could provide further evidence on the optimal treatment methods and length of excision for different transformation zone types. A network meta-analysis exploring these comparisons and the existing evidence base was published in 2022.

**Conclusion**

This Series paper introduces the terminology for cone and cervical dimensions proposed by ESGO, EFC, IFCPC, and ESP in 2022. It is recommended that this new terminology replace all existing terms in clinical and research settings. Professional bodies worldwide should disseminate this terminology and recommend that treatment centres, radiologists, and histopathologists should measure and report the three dimensions using standardised methods (anteroposterior dimension, transverse dimension, and length). Consistent use of the new terminology across settings would allow effective counselling in colposcopy clinics and accurate risk stratification in antenatal clinics, while making interventions more accurate and effective. Universally consistent reporting will facilitate improved communications between clinicians and pathologists, promote assessment of quality of practice and future research, and improve the quality of future meta-analyses.

**Contributors**

The manuscript was conceived by MK and EP. MK, MA, MG, and EP designed and led the work presented. The literature search was conducted
by MK and AA. Retrieved studies, personal experiences, and opinions were discussed among all authors. The manuscript was drafted by MK, AA, and EP, and was critically revised by all authors. All authors agreed with the results and conclusions presented in this Series paper.

Declaration of interests
We declare no competing interests.

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