



**UNIVERSIDADE ESTADUAL PAULISTA
“JÚLIO DE MESQUITA FILHO”
FACULDADE DE MEDICINA**

JOSÉ CÂNDIDO CALDEIRA XAVIER JÚNIOR

**RISCO ESTIMADO DAS LESÕES PRECURSORAS DO
COLO DO ÚTERO NOS EXAMES CITOLÓGICOS EM
FUNÇÃO DO TIPO DE LESÃO, INTERVALO ENTRE
OS CONTROLES E DA IDADE**

Tese apresentada à Faculdade de Medicina, Universidade Estadual Paulista “Júlio de Mesquita Filho”, Câmpus de Botucatu, para obtenção do título de Doutor em Patologia.

Orientadora: Profa. Dra. Rozany Mucha Dufloth
Coorientador: Prof. Dr. Luiz Carlos Zeferino

**Botucatu
2015**

José Cândido Caldeira Xavier Júnior

RISCO ESTIMADO DAS LESÕES PRECURSORAS
DO COLO DO ÚTERO NOS EXAMES
CITOLÓGICOS EM FUNÇÃO DO TIPO DE LESÃO,
INTERVALO ENTRE OS CONTROLES E DA IDADE

Tese apresentada à Faculdade de
Medicina, Universidade Estadual
Paulista “Júlio de Mesquita Filho”,
Câmpus de Botucatu, para obtenção
do título de Doutor em Patologia.

Orientadora: Profa. Dra. Rozany Mucha Dufloth
Coorientador: Prof. Dr. Luiz Carlos Zeferino

Botucatu
2015

FICHA CATALOGRÁFICA ELABORADA PELA SEÇÃO TÉC. AQUIS. TRATAMENTO DA INFORM.
DIVISÃO TÉCNICA DE BIBLIOTECA E DOCUMENTAÇÃO - CÂMPUS DE BOTUCATU - UNESP

BIBLIOTECÁRIA RESPONSÁVEL: ROSEMEIRE APARECIDA VICENTE-CRB 8/5651

Xavier Junior, Jose Candido Caldeira.

Risco estimado das lesões precursoras do colo do útero nos exames citológicos em função do tipo de lesão, intervalo entre os controles e da idade / Jose Candido Caldeira Xavier Junior.
- Botucatu, 2015

Tese (doutorado) - Universidade Estadual Paulista "Júlio de Mesquita Filho", Faculdade de Medicina de Botucatu

Orientador: Rozany Mucha Dufloth

Coorientador: Luiz Carlos Zeferino

Capes: 40105008

1. Hemorragia uterina. 2. Esfregaço vaginal. 3. Papanicolaou. 4. Vagina - Diagnóstico citológico. 5. Citologia.

Palavras-chave: Citologia; Esfregaço de Papanicolaou; Gestação; Idade; Sangramento uterino.

Ao Tio Marcinho (in memoriam), pela alegria de viver

Agradecimentos

A Deus pela realização de mais esse sonho

À Profa. Dra Rozany Mucha Dufloth pela oportunidade, paciência e por todos os ensinamentos concedidos

Ao Prof. Dr Luiz Carlos Zeferino pelo olhar clínico das nossas análises e por abrir as portas do CAISM-UNICAMP

À Profa. Dra Diama Bhadra Vale pelo apoio nesse trabalho colaborativo

Aos meus pais, minhas irmãs e demais familiares pela torcida e pelas orações

À Juliana pelo companheirismo

A todos os amigos, docentes e funcionários do Departamento de Patologia e Programa de Pós-graduação da UNESP – Botucatu e do CAISM - UNICAMP

"Somos como barcas
deslizando pelo tempo,
e nesse tempo
há que tecer a trama
da vida
com fios de amor e sonho,
para que a viagem seja leve,
para que a viagem seja bela"

Roseana Murray

Resumo

INTRODUÇÃO: A utilização do exame de citologia cérvico-vaginal para rastreamento do carcinoma do colo do útero diminuiu a incidência e mortalidade desse carcinoma e não há dúvidas que a identificação de lesões precursoras é importante nos cuidados com a saúde da mulher. Há poucos estudos sobre a associação do resultado de citologia cérvico-vaginal alterado em mulheres gestantes e mulheres com sangramento genital brasileiras. Além disso, ainda permanece controverso se as gestantes deveriam ser submetidas ao exame de citologia cérvico-vaginal como rotina do pré-natal e se a citologia cérvico-vaginal pode ser utilizada como método único de exclusão de neoplasia do colo do útero para as mulheres com informação clínica de sangramento genital.

OBJETIVOS: Estudar os fatores associados ao resultado do exame de citologia cérvico-vaginal alterado para mulheres gestantes e não-gestantes (idade, idade de início da atividade sexual, intervalo entre exames); e para mulheres com informação clínica de sangramento genital. **MÉTODOS:** Estudo observacional analítico que avaliou os resultados dos exames de citologia cérvico-vaginal encaminhados ao laboratório de Citopatologia Dr José Aristodemos Pinotti do Centro de Atenção Integrada à Saúde da Mulher da Universidade Estadual de

Campinas durante o período de Janeiro de 2000 a Dezembro de 2009 (10 anos) oriundos de mais de 70 municípios da região de Campinas, São Paulo - Brasil. O resultado do exame de citologia cérvico-vaginal foi reportado de acordo com o Sistema Bethesda. A partir dos formulários próprios da Instituição foram extraídos dados clínicos, citopatológicos e sociodemográficos necessários para a realização do presente estudo. **RESULTADOS:** Controlada a idade, idade de início da atividade sexual e intervalo entre exames não há diferença quanto a prevalência de lesão intraepitelial escamosa de alto grau entre mulheres gestantes e não-gestantes. No entanto, considerando a população estudada como um todo, intervalo entre os exames de citologia cérvico-vaginal maior ou igual a cinco anos e idade precoce de início da atividade sexual estão associados a maior chance de lesão intraepitelial escamosa de alto grau. Informação clínica de sangramento genital, para mulheres a partir de 30 anos, está associada a lesão intra-epitelial escamosa de alto grau, carcinoma de células escamosas e atipia de células glandulares; assim como está associada a adenocarcinoma, para mulheres a partir de 50 anos. Presença de informação clínica de sangramento genital está associada a maiores frequências de qualidade insatisfatória do esfregaço. **CONCLUSÃO:** os protocolos de coleta de exame de citologia cérvico-vaginal podem ser os mesmos para mulheres gestantes e não-gestantes; podendo a coleta não ser realizada de forma compulsória durante a gestação. Além disso, as mulheres com informação clínica de sangramento genital, principalmente àquelas a partir de 50 anos de idade, devem ser submetidas à avaliação pormenorizada para exclusão de neoplasia.

Símbolos, Siglas e Abreviaturas

CAISM	Centro de Atenção Integral à Saúde da Mulher
DNA	Ácido desoxirribonucléico (<i>deoxyribonucleic acid</i>)
HPV	Papilomavírus humano (<i>Human papillomavirus</i>)
HSIL	Lesão intraepitelial escamosa de alto grau (<i>High-grade squamous intraepithelial lesion</i>)
INCA	Instituto Nacional de Câncer
LSIL	Lesão intraepitelial escamosa de baixo grau (<i>Low-grade squamous intraepithelial lesion</i>)
NIC	Neoplasia intraepitelial cervical
SISCOLO	Sistema de Informação do Câncer do Colo do Útero
UNESP	Universidade Estadual Paulista
UNICAMP	Universidade Estadual de Campinas

Sumário

Capítulo I: Revisão da literatura	9
1.1.Introdução	10
1.2.Aspectos históricos	12
1.3.História natural do carcinoma do colo do útero	14
1.4.Epidemiologia	16
1.5.Fatores associados	18
1.6.Gestação	24
1.7.Sangramento genital	28
1.8.Diretrizes brasileiras para o rastreamento do carcinoma do colo do útero	33
1.9.Novas perspectivas	34
1.10.Referências bibliográficas	35
1.11.Objetivos	48
Capítulo II: Artigos científicos	49
Capítulo III: Conclusões	85

Capítulo I: Revisão da literatura

1.1. INTRODUÇÃO

O carcinoma do colo do útero é a segunda neoplasia mais comum entre as mulheres; sendo que 80% dos casos são estimados em países em desenvolvimento, devido à falta de programas de rastreamento bem estruturados baseados no exame de citologia cérvico-vaginal (Wu et al., 2014; Denny, 2012; Wiebe et al., 2012; Govindappagari et al., 2011; Schffman et al., 2007; Lowy & Schiler, 2006; Ronco et al., 2005; Waggoner, 2003).

A redução da mortalidade do carcinoma do colo do útero consequente à introdução do exame de rastreamento se deve ao aumento da detecção e abordagem terapêutica em estágios de lesão precursora (Canadian Task Force on Preventive Health Care et al., 2013; Saslow et al., 2012; Warren et al., 2009; Spence et al., 2007; Coleman & Poznansky, 2006; Kyrgiou et al., 2006; Ronco et al., 2005). No entanto, existe grande variação nas recomendações de cada país quanto ao público alvo que deveria realizar a coleta do exame de citologia cérvico-vaginal, bem como o intervalo entre exames que traria melhor benefício para as mulheres (Canadian Task Force on Preventive Health Care et al., 2013; Saslow et al., 2012; Anttila et al., 2009; Warren et al., 2009).

Nesse contexto, destaca-se a importância da colaboração entre os profissionais de saúde e as autoridades governamentais através de coordenação e planejamento de atividades de educação, comunicação e treinamento para superar as barreiras essenciais ao estabelecimento de programas de rastreamento do carcinoma do colo do útero capazes de atingir bom desempenho do exame de citologia cérvico-vaginal possibilitando tratamento das mulheres em estágios iniciais da doença (Wong et al., 2011;

Anttila et al., 2009).

Alguns fatores são considerados necessários para o sucesso do programa de rastreamento do carcinoma do colo do útero tais como: equipe de saúde bem treinada; cobertura abrangente da população-alvo em intervalos regulares (com mecanismo de convocação das mulheres); sistema de informação em saúde eficiente com gerenciamento e infraestrutura adequados; serviços de laboratório de escrutínio; programas de educação continuada; auditoria do laboratório por programas de controle de qualidade; acompanhamento e tratamento das mulheres, entre outros. A rigor, a inexistência de uma infraestrutura adequada para o funcionamento do sistema de rastreamento do carcinoma do colo do útero poderia justificar o fracasso desses programas em alguns países, principalmente naqueles ainda em desenvolvimento (Williams et al., 2014; Denny, 2012).

No Brasil, o Programa Nacional de Combate ao Câncer do Colo do Útero, instituído em 1998 pelo Ministério da Saúde, estabeleceu o Sistema de Informação do Câncer do Colo do Útero (SISCOLO) como importante ferramenta de monitoramento e gerenciamento das ações de saúde. No entanto, informações clínicas tais como gestação e sangramento genital não estão disponíveis na database do referido sistema o que tem impossibilitado a realização de pesquisas utilizando esses dados.

Além disso, ainda permanece controverso se as gestantes deveriam ser submetidas ao exame de citologia cérvico-vaginal como rotina do pré-natal e se a citologia cérvico-vaginal pode ser utilizada como método único de exclusão de neoplasia do colo do útero para as mulheres com informação clínica de sangramento genital. Trata-se de uma colaboração interinstitucional entre

Universidade Estadual Paulista (UNESP) e Universidade Estadual de Campinas (Unicamp) configurando parte de projeto de pesquisa desenvolvido nessa instituição (CEP Unicamp – 375/2010).

1.2. ASPECTOS HISTÓRICOS / CLASSIFICAÇÃO

O conceito da utilização da citologia esfoliativa para identificação de mulheres com carcinoma do colo do útero foi introduzida da década de 20 do século passado por Papanicolaou e Babes (Denny, 2012; Naylor 2000). Somente na década de 50, após revisão da técnica foi publicada a primeira classificação baseada em critérios citomorfológicos estabelecendo cinco categorias que tinham como parâmetro as células malignas do carcinoma invasor (Quadro 1) (Denny, 2012; Traut & Papanicolaou, 1943).

Quadro 1 : classificação do resultado do diagnóstico da citologia cérvico-cérvical

Classificação	Descrição
I	Ausência de células atípicas ou anormais
II	Atipia celular, ausência de evidência de malignidade
III	Citologia sugestiva, mas não conclusiva, de malignidade
IV	Citologia fortemente sugestiva de malignidade
V	Citologia conclusiva de malignidade

Fonte : Denny, 2012; Traut & Papanicolaou, 1943

O sistema Bethesda de classificação para resultado de citologia cérvico-vaginal, estabelecido a partir de 1988 e revisado em 2001, unificou a

interpretação e nomenclatura do resultado do exame de citologia cérvico-vaginal tornando-se, atualmente, a referência para o diagnóstico nos laboratórios de citopatologia no mundo e refletindo a compreensão mais atual da biologia desse tumor (Denny, 2012; Warren et al., 2009; Berek, 2003; Bethesda System, 1989).

O Sistema Bethesda também introduziu o conceito de esfregaço satisfatório como aquele que contém minimamente 8000 mil células escamosas e 10 células metaplásicas / endocervicais, considerando o esfregaço convencional. Além disso, o Sistema Bethesda estabeleceu classificação dicotômica das lesões precursoras em lesão intraepitelial escamosa de baixo grau (LSIL) e lesão intraepitelial escamosa de alto grau (HSIL). As lesões anteriormente classificadas em neoplasia intraepitelial cervical grau 1 (NIC 1) passaram a ser denominadas LSIL e a terminologia HSIL foi aplicada ao conjunto das lesões correspondentes a NIC 2 e NIC 3 (Solomon & Nayar, 2005; Bethesda System, 1989); sendo que atualmente somente a HSIL ou NIC3 seria considerada lesão precursora (Solomon & Nayar, 2005; Bethesda System, 1989).

Apesar da acurácia do exame de citologia cérvico-vaginal, alguns autores demonstram a existência de resultados falso negativos, principalmente decorrentes da baixa representatividade de células que possibilitem o diagnóstico de malignidade (Spence et al., 2007; Coleman & Poznasnsky, 2006) ou devido a artefatos que dificultam a visualização no microscópio óptico das células malignas; dentre estes encontram-se o excesso de hemácias, excesso de células inflamatórias e artefatos de dessecação do material (Ray & Kaul, 2008; Solomon & Nayar, 2005; Boon et al., 2003).

1.3. HISTÓRIA NATURAL DO CARCINOMA DO COLO DO ÚTERO

O colo do útero apresenta-se revestido por dois tipos diferentes de células epiteliais, sendo que a endocérvice tem revestimento epitelial de células cilíndricas mucossecretoras, e a ectocérvice por células escamosas. Por definição, a região de encontro entre estes dois epitélios é denominada zona de transformação devido a maior vulnerabilidade para as lesões neoplásicas. O fenômeno da metaplasia (transformação) ocorre mais frequentemente nessa região como resposta à agressão por processos inflamatórios e infecciosos, como o papilomavírus humano (HPV), por exemplo (Warren et al., 2009).

Dentro deste contexto, já está bem estabelecida a relação entre carcinoma do colo do útero e infecção persistente pelo HPV, ou seja, infecção detectada em mais de um exame de rastreamento com intervalo mínimo de seis meses (Brun-Micaleff et al., 2014; Saslow et al., 2012; Govindappagari et al., 2011; Warren et al., 2009; Bosch & Sanjosé, 2007; Lowy & Schiler, 2006). No entanto, destaca-se que os programas de rastreamento do carcinoma de colo do útero ainda não são capazes de atuar de forma efetiva no controle da infecção pelo vírus (Vale et al., 2013).

Estima-se que 50% de toda a população será infectada pelo HPV durante a vida (Govindappagari et al., 2011; Bosch & Sanjosé, 2007; Paavonen, 2007); sendo assim, a infecção pelo HPV tem sido doença sexualmente transmissível altamente prevalente na população geral (Hathaway, 2012; Bosch & Sanjosé, 2007; Sanjose et al., 2007). Evidencia-se em torno de 130 subtipos de HPV (Hathaway, 2012), sendo que os subtipos 16 e 18 são considerados os mais oncogênicos, identificados em

aproximadamente 70% de todos os casos de carcinoma de colo do útero ao redor do mundo (Paavonen, 2007; Sanjose et al., 2007; Clinfford 2006). O potencial oncogênico do vírus foi baseado na habilidade do ácido desoxirribonucleico (DNA) viral ser integrado ao genoma hospedeiro e controlar a regulação de genes nativos (Hathaway, 2012; Paavonen, 2007). Como resultado da infecção viral, a constante ativação das proteínas virais E6 e E7 leva a uma instabilidade genômica crescente, acúmulo de mutações no genoma com posterior perda do controle de crescimento celular, levando à transformação neoplásica (Hathaway, 2012; Paavonen, 2007).

O pico de incidência da infecção pelo HPV ocorre poucos anos após o início da atividade sexual sendo a maioria das infecções transitórias, tornando-se indetectáveis em um a dois anos (Hathaway, 2012; Saslow et al., 2012; Govindappagari et al., 2011; Ministério da Saúde, 2011; Rodriguez et al., 2010; Bano, et al., 2008; Paavonen, 2007; Lowy & Schiler, 2006; Moscicki et al., 2004). Dessa forma, visto que LSIL é compreendida como expressão morfológica da infecção transitória pelo vírus, essa categoria de lesão pode ser reconhecida como a representação indireta das frequências de infecção do HPV (Vale et al., 2013; Saslow et al., 2012; Govindappagari et al., 2011; Ministério da Saúde, 2011; Moscicki et al., 2010; Warren et al., 2009; Schffman et al., 2007; Lowy & Schiler, 2006; Vaccarella et al., 2006; Moscicki et al., 2004) e, por isso, apresentaria frequências mais elevadas na população mais jovem que, a princípio, poderia ser acompanhada de forma mais conservadora através do exame de citologia cérvico-vaginal a cada seis meses (Moscicki et al., 2010; Moscicki et al., 2004). Todavia, destaca-se que 30% das mulheres diagnosticadas com carcinoma do colo do útero estão em idade reprodutiva

(Van Calsteren et al., 2005).

A história natural da infecção pelo HPV apresenta redução significativa da incidência da infecção com o avançar da idade. No entanto, é partir da quarta / quinta década que se identifica associação com infecção persistente, indispensável para progressão para carcinoma (Rodriguez et al., 2010; Schffman et al., 2007).

Muitos outros fatores que em estudos anteriores estavam associados ao carcinoma do colo do útero, tais como número de parceiros sexuais, idade e uso de anticoncepcional oral e tabagismo (Jensen et al., 2013; Bano, et al., 2008; Vaccarella et al., 2006), atualmente são considerados como fatores indiretos associados à infecção pelo HPV (Jensen et al., 2013; Bosch & Sanjosé, 2007; Lowy & Schiler, 2006; Vaccarella et al., 2006; Kjellberg et al., 2000). Nesse contexto, as características clínicas e sociodemográficas estariam mais relacionadas ao processo de carcinogênese, ou seja, à transição da infecção do HPV de alto risco até o desenvolvimento da lesão precursora e posteriormente invasiva (Saslow et al., 2012; Govindappagari et al., 2011; Bosch & Sanjosé, 2007; Lowy & Schiler, 2006; Vaccarella et al., 2006; Muller & Smith, 2005); processo que pode ocorrer num período de dez a doze anos (Rodriguez et al., 2010; Anttila et al., 2009; Edelstein et al., 2009; Schffman et al., 2007; Snijders et al., 2006).

1.4. EPIDEMIOLOGIA

A prevalência de citologia cérvico-vaginal alterada não é uniforme variando de acordo com as particularidades de cada população estudada

(Coleman, 2013; Yang, 2012; Bano, et al., 2008; Bosch & Sanjosé, 2007; Frega et al., 2007; Vaccarella et al., 2006). Segue gráfico da incidência proporcional dos dez tipos de câncer mais frequentes na população feminina brasileira segundo dados do Instituto Nacional de Câncer José Alencar Gomes da Silva (INCA, 2014):

Figura 2: Distribuição proporcional dos dez tipos de câncer mais incidentes estimados para 2014 para o sexo feminino, exceto tumores de pele não melanoma

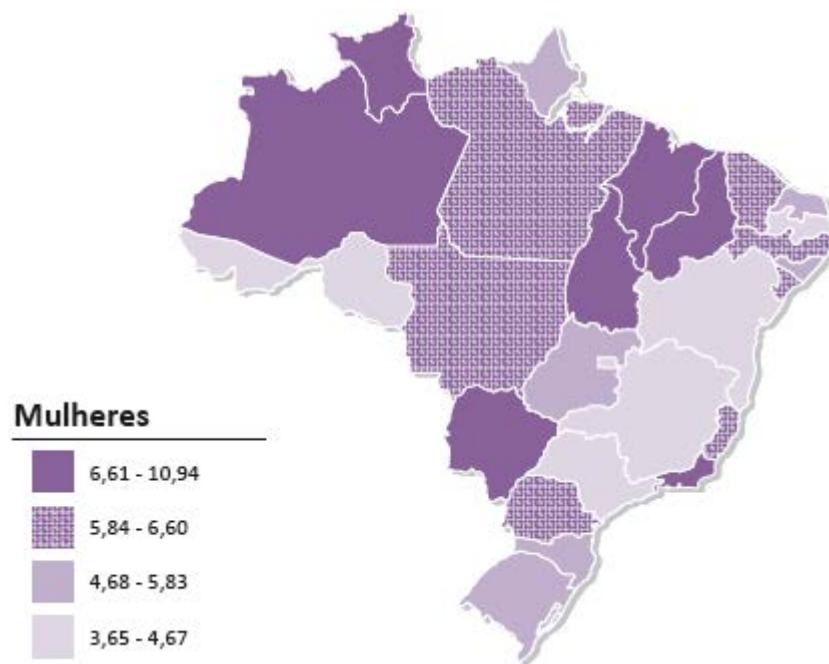
	Localização primária	casos	%
Mulheres 	Mama Feminina	57.120	20,8%
	Cólon e Reto	17.530	6,4%
	Colo do Útero	15.590	5,7%
	Traqueia, Brônquio e Pulmão	10.930	4,0%
	Glândula Tireoide	8.050	2,9%
	Estômago	7.520	2,7%
	Corpo do Útero	5.900	2,2%
	Ovário	5.680	2,1%
	Linfoma não Hodgkin	4.850	1,8%
	Leucemias	4.320	1,6%

Fonte: INCA, 2014

Segundo estimativas do INCA para o ano de 2014 são esperados 15.590 novos casos de carcinoma do colo do útero com risco estimado de 15,33 casos a cada 100 mil mulheres. A frequência do carcinoma do colo do útero pode ser interpretada como o retrato das desigualdades regionais observadas no Brasil. Com exceção dos tumores de pele não melanoma, o carcinoma do colo do útero configura o tumor de maior incidência na região norte, o segundo mais

frequente nas regiões nordeste e centro-oeste, o quarto mais frequente na região sudeste e o quinto mais frequente na região sul (INCA, 2014) (Figura 3).

Figura 3: Representação espacial das taxas brutas de incidência por 100 mil mulheres, estimadas para o ano de 2014, segundo Unidade da Federação (neoplasia maligna do colo do útero).



Fonte: INCA, 2014

1.5. FATORES ASSOCIADOS

Visto que o principal objetivo do programa de rastreamento é prevenir morbidade e mortalidade por câncer, define-se como estratégia de rastreamento do carcinoma do colo do útero aquela capaz de identificar as lesões mais prováveis de evoluir para carcinoma invasivo e evitar a detecção e tratamento desnecessário de lesões transitórias (Canadian Task Force on Preventive Health Care et al., 2013; Saslow et al., 2012).

Ao mesmo tempo, vislumbra-se um programa de rastreamento no qual potenciais pontos negativos tais como gastos públicos com número de exames excessivos ou tratamento desnecessário em mulheres com resultados falso-negativos sejam minimizados (Canadian Task Force on Preventive Health Care et al., 2013).

Nesse contexto, destaca-se a importância do presente estudo que avaliou possível associação da idade, intervalo entre exames e informações clínicas de gestação e sangramento genital com o carcinoma do colo do útero.

1.5.1 Idade das pacientes

As recomendações quanto à idade de início do exame de rastreamento do carcinoma do colo do útero pela citologia cérvico-vaginal variam de 18 a 35 anos (Canadian Task Force on Preventive Health Care et al., 2013; Saslow et al., 2012; Anttila et al., 2009; Warren et al., 2009). Nos países Europeus a idade do público-alvo dos programas de rastreamento varia de 20 a 30 anos estendendo-se até os 60 a 70 anos (Anttila et al., 2009). Por outro lado, as recomendações canadenses estabelecem que não existe benefício para a primeira coleta do exame de citologia cérvico-vaginal em idade inferior a 25 anos e que os exames devem ser interrompidos a partir dos 70 anos após pelo menos três resultados anteriores negativos (Canadian Task Force on Preventive Health Care et al., 2013).

Recomendações americanas preconizam que o exame de citologia cérvico-vaginal seja realizado a partir dos 21 anos. Para as mulheres a partir de 65 anos com história patológica pregressa negativa (três exames de citologia cérvico-vaginal negativos ou dois exames simultâneos negativos – citologia

cérvico-vaginal e pesquisa de HPV - sendo o último exame realizado dentro dos últimos cinco anos) e na ausência de resultado de citologia cérvico-vaginal progresso de NIC 2 ou categoria de lesão mais grave, não é preconizada nenhuma modalidade de exame de rastreamento (Saslow et al., 2012).

Destaca-se que a frequência de resultado de exame de citologia cérvico-vaginal alterado em pacientes menores que 25 anos não é insignificante (Moscicki et al., 2010); aproximadamente 34% das pacientes referenciadas ao exame colposcópico apresentaram lesão intraepitelial escamosa de alto grau (NIC 2 e NIC 3), confirmada histologicamente (Bano, et al., 2008). No entanto, para a população abaixo de 30 anos a categoria HSIL apresenta alta frequência de NIC 2, que pode ser interpretada como representação da infecção transitória pelo HPV nas pacientes fora dos programas de rastreamento (Vale et al., 2013).

Estudo inglês avaliando as características das mulheres com carcinoma do colo do útero entre 20 e 29 anos indicou tratar-se de casos em estágio inicial, com excelente prognóstico, sendo frequentemente identificado no primeiro exame de citologia cervico-vaginal da mulher. Além disso, destaca-se que apesar do carcinoma do colo do útero ser muito raro em idade inferior a 25 anos (apenas 12% dos casos diagnosticados no grupo etário em estudo), as frequências desse carcinoma dos 25 aos 29 anos tem apresentado aumento (Castanon et al., 2013).

Sugere-se que o rastreamento do carcinoma do colo do útero possa reduzir a incidência de câncer entre as mulheres de 20 a 24 anos; no entanto, influência nas frequências de mortalidade apenas é observada quando o

exame de rastreamento se inicia no grupo etário de 25 a 29 anos (Popadiuk et al., 2012), talvez devido à raridade de casos em idade inferior a 25 anos. Nesse contexto, destaca-se que ainda não existe embasamento suficiente, na literatura, para a realização de exame de rastreamento em mulheres com idade inferior aos 21 anos (Moscicki 2010), sendo recomendado acompanhamento conservador, para as lesões precursoras de baixo grau, nos grupos etários mais jovens (Castanon et al., 2013; Moscicki 2010; Campbell & Lara-Torre, 2009).

Por outro lado, a realização do exame de citologia cérvico-vaginal em mulheres jovens e adolescentes pode desencadear uma rotina ao longo da vida da mulher. Dentro deste contexto, as lesões precursoras poderiam ser diagnosticadas precocemente contribuindo para a redução da incidência do carcinoma do colo do útero (Castanon et al., 2013; Popadiuk et al., 2012).

1.5.2 Intervalo entre exames

Apesar do benefício do exame de citologia cérvico-vaginal ser inquestionável, ainda permanece controverso o intervalo ideal entre os exames e, por definição, preconiza-se que o intervalo entre exames deva ser estabelecido de forma que o desenvolvimento de carcinoma invasivo seja altamente improvável até que ocorra a realização próximo exame de citologia cérvico-vaginal (Saslow et al., 2012).

Nos países europeus o intervalo entre os exames varia de um a cinco anos; sendo que há um consenso de que três anos seja o intervalo adequado (Anttila et al., 2009), à semelhança das recomendações canadenses (Canadian

Task Force on Preventive Health Care et al., 2013).

Segundo as recomendações americanas para rastreamento de carcinoma do colo do útero, para as mulheres de 21 a 29 anos o exame de citologia cérvico-vaginal a cada três anos é preconizado como método único; sendo que, para mulheres entre 30 e 65 anos também existe a possibilidade de realização simultânea de exame de citologia cérvico-vaginal e teste para pesquisa de HPV a cada cinco anos.

Estudo realizado no Reino Unido mostrou que o intervalo entre exames de citologia cérvico-vaginal deve variar de acordo com os grupos etários. Para mulheres entre 20 e 39 anos o exame de rastreamento anual não atingiu 80% efetividade; sendo que, três anos após a realização do exame de citologia cérvico-vaginal, a incidência do carcinoma do colo do útero se assemelha a encontrada nas mulheres fora dos programas de rastreamento. Para mulheres entre 40 e 54 anos as taxas de efetividade entre rastreamento anual e a cada três anos são muito semelhantes (88% e 84%, respectivamente). Já para mulheres entre 55 e 69 anos a realização da coleta do exame de citologia cérvico-vaginal a cada cinco anos atingiu proteção de 83%. Assim sendo, este estudo mostrou que o exame de rastreamento do carcinoma do colo do útero pode ser realizado a partir dos 25 anos com intervalo de três anos até os 49 anos e intervalo de cinco anos no grupo etário de 50 a 64 anos (Sasieni et al., 2003).

1.5.3 Idade de início da atividade sexual

O intervalo entre a idade de início da atividade sexual e o diagnóstico de carcinoma do colo do útero varia de 4 a 35 anos (Edelstein et al., 2009),

podendo existir associação entre idade de início da atividade sexual e carcinoma do colo do útero (Plummer et al., 2012; Louie et al., 2009) através de uma relação logarítmica não linear (Plummer et al., 2012). Alguns autores mostram que há maior vulnerabilidade da junção escamo-colunar à infecção pelo HPV em populações mais jovens (Plummer et al., 2012; Louie et al., 2009; Schffman et al., 2007). Por outro lado, outros autores, utilizando análise multivariada ajustada à infecção pelo HPV, indicaram que a idade de início da atividade sexual não apresentou associação com o carcinoma do colo do útero (Kjellberg et al., 2000).

Estudo transnacional sobre a relação entre idade de início da atividade sexual e carcinoma do colo do útero revelou que mulheres que iniciaram a vida sexual em idade igual ou inferior a 16 anos possuem aproximadamente 2,5 vezes maior risco de apresentar carcinoma do colo do útero do que as mulheres com idade de início da atividade sexual igual ou maior que 21 anos (Louie et al., 2009). Estudo chinês que propõem associação entre resultado de citologia cérvico-vaginal alterado e início de atividade sexual anterior aos 18 anos corrobora a relação entre carcinoma do colo do útero e idade precoce de início da atividade sexual (Wong et al., 2011); associação que pode ser interpretada como reflexo dos fatores associados à infecção pelo HPV (Edelstein et al., 2009).

Sugere-se também que as mulheres com idade de início da atividade sexual mais precoce seriam as mesmas que precocemente tornam-se gestantes visto que mais de 60% das mulheres afirmam dar a luz ao primeiro filho no prazo menor que um ano após o início da atividade sexual (Louie et al., 2009).

1.6. GESTAÇÃO

Levando-se em conta que a maioria das gestações ocorre dos 18 aos 35 anos; e que este grupo etário correspondente às maiores taxas de detecção de neoplasia intraepitelial cervical (Frega et al., 2007; Kaplan et al., 2004; Muller & Smith, 2005), a gestação pode representar uma oportunidade de entrada das mulheres nos programas de rastreamento do carcinoma do colo do útero (Coleman, 2013; Yang, 2012; Fader et al., 2010; Frega et al., 2007; Muller & Smith, 2005; Van Calsteren et al., 2005); embora alguns autores considerem que as frequências de resultado de citologia cérvico-vaginal alterado não variem entre mulheres gestantes e não-gestantes (Fader et al., 2010; Lee et al., 2008).

A coleta do exame de citologia cérvico-vaginal pode ser realizada durante a gestação, não apresentando riscos para a mulher nem para o feto, mesmo que se realize a coleta da região endocervical (Govindappagari et al., 2011; Hunter et al., 2008; Lee et al., 2008). No entanto, na interpretação do exame de citologia cérvico-vaginal em mulheres gestantes, deve-se levar em conta as alterações próprias da gestação tais como: presença de células deciduais, inflamação, reação de Arias-Stella e células metaplásicas imaturas (Stonehocker, 2013; Morice et al., 2012; McIntyre-Seltman & Lesnock, 2008; Coleman & Poznansky, 2006; Brown et al., 2005; Muller & Smith, 2005; Lu et al., 2003; Broderick et al., 2002). Essas alterações próprias da gestação não devem ser interpretadas como atípicas ou lesões precursoras e o citopatologista deve estar ciente que se trata de mulher gestante, ressaltando a importância das informações clínicas e salientando-se que a interpretação dos critérios

citológicos são os mesmos para as mulheres gestantes e não-gestantes (Bond, 2009).

Estima-se que 1% a 5% das gestantes apresentem resultado de exame citologia cérvico-vaginal alterado, sendo que a incidência de carcinoma do colo do útero mostra uma variação de um a doze casos para cada 100 mil gestações (Wu et al., 2014; Morice et al., 2012; Yang, 2012; Bond, 2009; McIntyre-Seltman & Lesnock, 2008; Brown et al., 2005; Kaneshiro et al., 2005; Van Calsteren et al., 2005; Palle et al., 2000), caracterizando uma das neoplasias mais frequentemente diagnosticadas durante a gravidez (Morice et al., 2012; Govindappagari et al., 2011; Bond, 2009; Onuma et al., 2006; Brown et al., 2005; Van Calsteren et al., 2005; Kaplan et al., 2004).

O exame de citologia cérvico-vaginal foi anteriormente estabelecido como rotina do pré-natal na tentativa de aumentar os índices de detecção de lesões precursoras do carcinoma do colo do útero (Hunter et al., 2008). No entanto, atualmente, é sugerido que as gestantes sejam submetidas ao exame de citologia cérvico-vaginal de acordo com os protocolos vigentes para as mulheres não-gestantes (Stonehocker, 2013; Saslow et al., 2012; Ministério da Saúde, 2011).

Em estudo francês avaliando mulheres gestantes com baixa adesão ao programa de rastreamento e média de idade de 25 anos, identificou-se frequência de resultado de exame de citologia cérvico-vaginal alterado em cerca de 3,6 %, sendo que 20,2 % das gestantes apresentaram positividade para DNA de HPV de alto-risco (Brun-Micaleff et al., 2014).

Apesar de a gestação ser considerada um momento de imunossupressão

ainda permanece controversa a relação da gravidez com o carcinoma de colo do útero e, a rigor, a história natural dessa neoplasia pode não ser influenciada pela gestação (Yang, 2012; Frega et al., 2007; Van Calsteren et al., 2005; Kaplan et al., 2004; Lu et al., 2003; Paraskevidis et al., 2002; Kjellberg et al., 2000; Palle et al., 2000) ou pelo tipo de parto, seja vaginal ou cesariana (Kaneshiro et al., 2005).

Estudo comparando mulheres gestantes e não-gestantes com carcinoma do colo do útero em estadiamento precoce demonstrou que não existe diferença quanto a fatores de risco, prognóstico e sobrevida total. No entanto, ao contrário das mulheres não-gestantes, as mulheres gestantes não apresentam associação entre profundidade de invasão tumoral com acometimento linfovascular ou linfonodal (Lee et al., 2008).

Apesar das mulheres gestantes jovens constituírem um grupo com maior paridade e maior chance de infecção pelo HPV (Hunter et al., 2008), estudos mostram que a mulheres gestantes quando comparadas às mulheres não-gestantes não apresentam diferença na frequência de infecção pelo vírus bem como na história natural da infecção pelo HPV (Muller & Smith, 2005; Lu et al., 2003). Além disso, demonstrou-se menor frequência de carcinoma de colo do útero e HSIL entre as mulheres gestantes em comparação às mulheres não-gestantes com diagnóstico de atipias de células escamosas de significado indeterminado (Broderick et al., 2002) e atipias de células escamosas não podendo excluir lesão intraepitelial escamosa de alto grau (Onuma et al., 2006).

A rigor, espera-se que durante a gravidez a maioria dos casos de LSIL

regredida ou permaneça estável enquanto os casos de HSIL poderão regredir, persistir ou até mesmo progredir para carcinoma invasivo (Wu et al., 2014; Fader et al., 2010; Van Calsteren et al., 2005; Kaplan et al., 2004; Paraskevaïdis et al., 2002). Destaca-se estimativa de que no período pós-parto possa ocorrer regressão de LSIL, estando associada à ausência de história de tabagismo (Fader et al., 2010). Todavia, um estudo mostrou que mulheres gestantes com diagnóstico de LSIL e HSIL apresentam maior frequência de recorrência de doença em cinco anos (Kaplan et al., 2004).

Em estudo realizado com mulheres infectadas por HPV de sorotipos de alto risco, a gestação completa foi considerada como fator de risco para desenvolvimento de carcinoma do colo do útero a partir de existência de lesões precursoras, o que não foi observado com relação ao uso de contraceptivo oral e ao comportamento sexual (idade de início da atividade sexual e número de parceiros) (Jensen et al., 2013). Por outro lado, estudo chinês observou associação entre resultado de citologia cérvico-vaginal alterado e número de gestações, número de abortos e número de filhos (Wong et al., 2011). Dessa forma, discute-se se a gestação e/ou o parto poderiam ter alguma influência na história natural do carcinoma do colo do útero.

As gestantes com resultado de exame de citologia cérvico-vaginal alterado devem ser encaminhadas a médicos especialistas a fim de serem submetidas à abordagem diagnóstica complementar com exame de colposcopia, biópsia e, quando necessário, acompanhamento da mulher no período pós-parto (Wu et al., 2014; Yang, 2012; Fader et al., 2010; Bond, 2009; Brown et al., 2005; Muller & Smith, 2005; Van Calsteren et al., 2005; Broderick et al., 2002; Palle et al., 2000). Por outro lado, estudos mostraram que mesmo

os tratamentos considerados conservadores, como a conização, estão associados a morbidades tais como parto prematuro e recém-nascido com baixo peso (Moscicki, 2010; Kyrgiou et al., 2006). Por isso, na grande maioria dos casos, as gestantes com resultado de exame de citologia cérvico-vaginal alterado são acompanhadas de forma conservadora até o período pós-parto (Yang, 2012; Muller & Smith, 2005); devendo cada caso ser avaliado de forma individualizada, por equipe multidisciplinar, considerando o bem-estar da gestante e do feto (Wiebe et al., 2012; Yang, 2012).

1.7. SANGRAMENTO GENITAL

O sangramento genital configura uma queixa médica frequente entre as mulheres (Selo-Ojeme et al., 2014; Shapley et al., 2004; Farquhar et al., 2003) devendo ser investigado para exclusão de neoplasia (Ray & Kaul, 2008). Várias são as causas de sangramento genital, entre elas estão a presença de pólipos, ectopia cervical e neoplasias invasivas cervicais, endometriais ou vaginais (Selo-Ojeme et al., 2014; Kaur et al. 2010; Alfhaily & Ewies, 2009; Tehranian et al., 2009; Ray & Kaul, 2008; Shapley et al., 2006; Rosenthal et al., 2001). Sangramento uterino anormal tem ocorrido em onze a treze por cento na população geral, apresentando elevação da frequência nas mulheres com o aumento da idade, chegando a corresponder a 24% das mulheres nas faixas estárias de 36 a 40 anos (Marret et al., 2010).

Existe certa divergência entre os autores sobre a definição de sangramento genital, podendo corresponder a menometrorragia, sangramento pós-coito, sangramento intermenstrual, sangramento peri e pós-menopausa. Por se tratar de uma queixa subjetiva ainda não tem sido possível avaliar as

queixas menstruais por critérios objetivos que possam ser reproduzidos nas pesquisas (Shapley et al., 2006; Shapley et al., 2004). Além disso, muitas doenças podem ter como queixa inicial o sangramento genital a depender do grupo populacional estudado e da faixa etária considerada (Marret et al., 2010; Shapley et al., 2004). Atualmente, os sintomas de sangramento genital tem sido relacionados principalmente às alterações hormonais femininas, sendo o carcinoma do colo do útero a neoplasia mais associada a essa sintomatologia (Viikki et al., 1998).

Define-se como sangramento pós-coito aquele que ocorre durante ou imediatamente após a relação sexual e fora do período menstrual (Alfhaily & Ewies, 2009; Tehranian et al., 2009). Observa-se associação estatística entre sangramento pós-coito e resultado de citologia cérvico-vaginal alterado (Wong et al., 2011), sendo identificadas lesões correspondentes a NIC 2 e NIC 3 em 12% das mulheres com queixa de sangramento pós-coito (Rosenthal et al., 2001).

Na atenção primária a queixa de sangramento pós-coito foi estimada em torno de 0,7% a 9% (Shapley et al., 2006). Entre as mulheres com carcinoma do colo do útero a queixa de sangramento pós-coito variou de 0,7% a 39% (Shapley et al., 2006; Rosenthal et al., 2001), sendo que o risco relativo de carcinoma invasivo para as mulheres com sangramento pós-coito foi cerca de seis vezes o risco das mulheres sem queixas de sangramento genital (Shapley et al., 2006).

Comparando dois grupos de mulheres com sangramento pós-coito as mulheres com neoplasias malignas e suas lesões precursoras e mulheres com doenças benignas, não foi observada diferença estatística quanto a fatores

sociodemográficos como tabagismo, número de parceiros sexuais, idade de início da atividade sexual (Tehrani et al., 2009), apesar de um estudo mostrar que possa ocorrer associação entre sangramento pós-coito na faixa etária mais jovem (Shapley et al., 2004).

Uma a cada doze mulheres com sangramento pós-coito e citologia cérvico-vaginal negativa apresenta alterações histológicas correspondentes a malignidades ou lesões precursoras (Jha & Sbarwal, 2002); enfatizando que a informação clínica de sangramento pós-coito possui relevância diagnóstica, uma vez que muitas lesões precursoras (HSIL) foram identificadas em exame colposcópico apesar do resultado negativo da citologia cérvico-vaginal (Tehrani et al., 2009; Rosenthal et al., 2001). Nesse contexto, visto que apenas 55% das alterações do exame histopatológico foram identificadas no exame de citologia cérvico-vaginal das mulheres com sangramento pós-coito questiona-se a utilização da citologia cérvico-vaginal como método diagnóstico único de avaliação das mulheres com a referida queixa (Jha & Sbarwal, 2002).

Por outro lado, destaca-se que não foi observada associação significativa entre a sintomatologia de sangramento genital e carcinoma do colo do útero invasivo num estudo que teve seguimento clínico de cinco anos em mulheres que apresentaram resultado de citologia cérvico-vaginal negativa (Kotaniemi-Talonen et al., 2011), reforçando a importância do papel do exame de citologia cérvico-vaginal nesses casos.

Nesse contexto, a informação clínica de sangramento genital possui relevância no diagnóstico, pois a presença de hemácias lisadas no fundo do esfregaço tem sido considerado como critério para o diagnóstico citológico de

neoplasias invasivas (Solomon & Nayar, 2005; Boon et al., 2003); podendo ser interpretada como consequência do processo de angiongênese tumoral que induz proliferação capilar (Boon et al., 2003).

Por outro lado, levando-se em conta os critérios citológicos definidos no sistema Bethesda de classificação, os esfregaços com presença de excesso de hemácias podem ser classificados como amostra de qualidade insatisfatória quando mais de 75% das células escamosas encontram-se obscurecidas pela grande quantidade de hemácias (Solomon & Nayar, 2005; Bethesda System, 1989). Entretanto, esses esfregaços requerem atenção minuciosa, pois se forem observadas células atípicas, a amostra não deve ser categorizada como insatisfatória (Coleman & Poznasnsky, 2006; Solomon & Nayar, 2005). Ressalta-se que esfregaço com qualidade insatisfatória pode representar atraso no diagnóstico de neoplasias malignas e possível perda da oportunidade de acompanhamento destas mulheres, que por diversas razões, muitas vezes não retornam para repetir a coleta do exame de citologia cérvico-vaginal (Boon et al., 2003).

Apesar do exame de colposcopia ser parte do programa de rastreamento do carcinoma do colo do útero para avaliação das mulheres com resultado de citologia cérvico-vaginal alterado (Ray & Kaul, 2008), o sangramento pós-coito como sintoma único, não é indicação absoluta para referência ao exame colposcópico (Alfhaily & Ewies, 2009; Tehranian et al., 2009). No entanto, visto que quase a totalidade das mulheres com sangramento pós-coito são encaminhadas para a colposcopia, tem sido observada sobrecarga na demanda de profissionais especializados (See & Havenga, 2013).

Os diagnósticos de carcinoma e hiperplasia endometrial têm sido os mais frequentes em mulheres com queixa clínica de sangramento genital na pós e perimenopausa (Kaur et al. 2010). A rigor, a informação clínica de sangramento genital torna-se importante porque a presença de células endometriais normais em mulheres na pós-menopausa com queixa de sangramento não é fator preditor de câncer endometrial; ao passo que a presença de células endometriais atípicas aumenta a chance de resultado de citologia cérvico-vaginal de carcinoma endometrial (Van Doorn et al., 2009).

Segundo o programa de rastreamento de carcinoma do colo do útero dos serviços de saúde o Reino Unido, as mulheres com sangramento pós-coito e com idade superior a 40 anos e mulheres com presença de sangramento vaginal devem ser avaliadas por ginecologista e serem submetidas ao exame colposcópico quando houver suspeita de neoplasia maligna, independente do resultado de citologia cérvico-vaginal (National Health Service Cervical Screening Programme, 2010; Tehranian et al., 2009).

A revisão da literatura mostrou poucos estudos sobre a possível associação entre o sintoma do sangramento genital e o diagnóstico histopatológico. Assim sendo, o entendimento das causas de sintoma de sangramento genital pode permitir a formulação de protocolos mais específicos e o estabelecimento de políticas públicas de saúde que visem eficiência diagnóstica e redução de gastos.

1.8. DIRETRIZES BRASILEIRAS PARA O RASTREAMENTO DO CARCINOMA DO COLO DO ÚTERO (Ministério da Saúde, 2011)

Entende-se o programa de rastreamento do carcinoma do colo do útero como um processo multifatorial complexo que vai desde a realização do exame de rastreamento, identificação dos casos positivos, confirmação diagnóstica e tratamento. Todavia, apesar dos esforços do Ministério da Saúde, ainda não existe no Brasil programa organizado que permita identificar as mulheres que realizam os exames e a periodicidade que o fazem.

No Brasil o exame de citologia cérvico-vaginal tem sido priorizado para mulheres na faixa etária de vinte e cinco a sessenta e quatro anos com a periodicidade de realização do exame uma vez ao ano; sendo que, se a mulher apresentar dois resultados de exames de citologia cervico-vaginal negativos, recomenda-se repetição do exame a cada três anos. A interrupção de rastreamento do carcinoma do colo do útero ocorrerá aos sessenta e quatro anos na presença de pelo menos dois exames de citologia cérvico-vaginal consecutivos progressivos negativos para lesão intraepitelial e malignidades nos últimos cinco anos. Para as mulheres a partir do sessenta e quatro e que nunca realizaram este exame, a conduta preconizada tem sido realizar dois exames de citologia cérvico-vaginal com intervalo de um a três anos; sendo os exames negativos para lesão intraepitelial e malignidades, a mulher não precisaria continuar no programa de rastreamento do carcinoma do colo do útero. Visto que se trata de um sistema oportunístico de rastreamento; as mulheres, quando desejarem, podem ser submetidas ao exame de citologia cérvico-vaginal ainda que estejam fora do público-alvo preconizado, por exemplo, mulheres com idade abaixo de 25 anos e acima de 64 anos.

Para as mulheres gestantes, o programa de rastreamento do carcinoma do colo do útero apresenta recomendações semelhantes às das mulheres não-gestantes, ressaltando-se o pré-natal como uma oportunidade para a entrada da mulher no programa de rastreamento. Além disso, destaca-se a ausência de recomendações específicas para mulheres com sangramento genital nas diretrizes deste programa.

1.9. NOVAS PERSPECTIVAS

Atualmente a introdução de vacinas contra-HPV em mulheres jovens dentre as políticas pública de saúde vislumbra uma possível redução nas taxas de infecção pelo vírus (Paavonen, 2007; Schffman et al., 2007; Lowy & Schiler, 2006). Como entraves logísticos à efetividade da vacinação têm sido destacada a dificuldade de completar o ciclo de três vacinações e a abordagem diagnóstica da população pré-pubere antes do contato com o vírus (Moscicki et al., 2010). É necessário ressaltar que, mesmo após a vacinação, as mulheres deverão continuar a ser submetidas aos exames de rastreamento do carcinoma do colo do útero uma vez que as vacinas são focadas apenas nos sorotipos de HPV de alto risco (Saslow et al., 2012; Lowy & Schiler, 2006). Portanto, permanece desconhecido o real impacto da vacinação na prevalência do carcinoma do colo do útero nas populações vacinadas (Plummer et al., 2012; Schffman et al., 2007) tão bem como o custo financeiro da utilização da vacina em larga escala na população (Schffman et al., 2007).

Até o momento considera-se que o exame de citologia cérvico-vaginal convencional e o exame de citologia em meio líquido possuem sensibilidade e especificidade semelhantes quando comparados para detecção das lesões

precursoras (Saslow et al., 2012; Siebers et al, 2009), principalmente HSIL (Sigurdsson et al., 2013; Saslow et al., 2012; Ministério da Saúde, 2011). Além disso, nenhum teste para HPV disponível foi identificado como método padrão para rastreamento do carcinoma do colo do útero, quando considerado como exame exclusivo (Saslow et al., 2012; Ministério da Saúde, 2011).

Devido à alta sensibilidade do exame de citologia cérvico-vaginal os países com programas de rastreamento do carcinoma do colo do útero bem estruturados, como o Canadá, ainda consideram prematura a introdução do teste do HPV como única forma de rastreamento ou em associação com o exame de citologia cérvico-vaginal (Canadian Task Force on Preventive Health Care et al., 2013).

Pesquisas futuras são necessárias para avaliar as vantagens e desvantagens do maior intervalo entre exames de citologia após a incorporação do teste de pesquisa de HPV; tendo em vista chance de aumento do número de exames colposcópicos devido a elevada incidência de infecção pelo vírus, muitas vezes transitória (Canadian Task Force on Preventive Health Care et al., 2013). Dessa forma, destaca-se que, para redução da incidência do carcinoma do colo do útero são necessários esforços adicionais, focados em educação sexual e planejamento familiar, adequados à extrema variação sociocultural dos mais diversos países do mundo (Louie et al., 2009).

1.10. REFERÊNCIAS BIBLIOGRÁFICAS

Alfhaily F, Ewies AA. Postcoital bleeding: A study of the current practice amongst consultants in the United Kingdom. Postcoital bleeding: a study of the

current practice amongst consultants in United Kingdom. *Eur J Obstet Gynecol Reprod Biol.* 2009; 144(1):72-5.

Anttila A, von Karsa L, Aasmaa A, Fender M, Patnick J, Rebolj M, Nicula F, Vass L, Valerianova Z, Voti L, Sauvaget C, Ronco G. Cervical cancer screening policies and coverage in Europe. *Eur J Cancer.* 2009; 45(15):2649-58.

Bano F, Kolhe S, Zamblera D, Jolaoso A, Folayan O, Page L, Norton J. Cervical screening in under 25s: a high-risk young population. *Eur J Obstet Gynecol Reprod Biol.* 2008; 139(1):86-9.

Berek JS. Simplification of the new Bethesda 2001 classification system. *Am J Obstet Gynecol.* 2003; 188(3 Suppl):S2-5.

Bond S. Caring for women with abnormal papanicolaou tests during pregnancy. *J Midwifery Womens Health.* 2009; 54(3):201-10.

Boon ME, Ouwerkerk-Noordam E, van Leeuwen AW, van Haften-Day C. Clinical and diagnostic significance of blood in cervical smears. *Diagn Cytopathol.* 2003; 28(4):181-5.

Bosch FX, de Sanjosé S. The epidemiology of human papillomavirusinfection and cervical cancer. *Dis Markers.* 2007; 23(4):213–27.

Broderick D, Matityahu D, Dudhbhai M, Alter S. Histologic and colposcopic correlates of ASCUS pap smears in pregnancy. *J Low Genit Tract Dis.* 2002; 6(2):116-9.

Brown D, Berran P, Kaplan KJ, Winter WE 3rd, Zahn CM. Special situations: abnormal cervical cytology during pregnancy. *Clin Obstet Gynecol.* 2005; 48(1):178-85.

Brun-Micaleff E, Coffy A, Rey V, Didelot MN, Combecal J, Doutre S, Daurès JP, Segondy M, Boulle N. Cervical cancer screening by cytology and human papillomavirus testing during pregnancy in French women with poor adhesion to regular cervical screening. *J Med Virol.* 2014; 86(3):536-45.

Campbell FN, Lara-Torre E. Follow-up compliance of adolescents with cervical dysplasia in an inner-city population. *J Pediatr Adolesc Gynecol.* 2009; 22(3):151-5.

Canadian Task Force on Preventive Health Care, Dickinson J, Tsakonas E, Conner Gorber S, Lewin G, Shaw E, Singh H, Joffres M, Birtwhistle R, Tonelli M, Mai V, McLachlin M. Recommendations on screening for cervical cancer. *CMAJ.* 2013; 185(1):35-45.

Castanon A, Leung VM, Landy R, Lim AW, Sasieni P. Characteristics and screening history of women diagnosed with cervical cancer aged 20-29 years. *Br J Cancer.* 2013; 109(1):35-41.

Coleman CA. Evaluation and management of abnormal cervical cytology during pregnancy. *Clin Obstet Gynecol.* 2013; 56(1):51-4.

Coleman DV, Poznansky JJ. Review of cervical smears from 76 women with invasive cervical cancer: cytological findings and medicolegal implications. *Cytopathology.* 2006; 17(3):127-36.

Denny L. Cytological screening for cervical cancer prevention. *Best Pract Res Clin Obstet Gynaecol.* 2012; 26(2):189–96.

Edelstein ZR, Madeleine MM, Hughes JP, Johnson LG, Schwartz SM, Galloway DA, Carter JJ, Koutsky LA. Age of diagnosis of squamous cell cervical carcinoma and early sexual experience. *Cancer Epidemiol Biomarkers Prev.* 2009; 18(4):1070-6.

Fader AN, Alward EK, Niederhauser A, Chirico C, Lesnock JL, Zwiesler DJ, Guido RS, Lofgren DJ, Gold MA, Moore KN. Cervical dysplasia in pregnancy: a multi-institutional evaluation. *Am J Obstet Gynecol.* 2010; 203(2):113.e1-6.

Farquhar C, Ekeroma A, Furness S, Arroll B. A systematic review of transvaginal ultrasonography, sonohysterography and hysteroscopy for the investigation of abnormal uterine bleeding in premenopausal women. *Acta Obstet Gynecol Scand.* 2003; 82(6):493-504.

Frega A, Scirpa P, Corosu R, Verrico M, Scarciglia ML, Primieri MR, Palazzo A, Iacovelli R, Moscarini M. Clinical management and follow-up of squamous intraepithelial cervical lesions during pregnancy and postpartum. *Anticancer Res.* 2007; 27(4C):2743-6.

Govindappagari S, Schiavone MB, Wright JD. Cervical neoplasia. *Clin Obstet Gynecol.* 2011; 54(4):528-36.

Hunter MI, Monk BJ, Tewari KS. Cervical neoplasia in pregnancy. Part 1: screening and management of preinvasive disease. *Am J Obstet Gynecol.* 2008; 199(1):3–9.

Instituto Nacional de Câncer José Alencar Gomes da Silva (Brasil). Estimativa 2014. Incidência do Câncer no Brasil. Rio de Janeiro: INCA; 2014.

Jha S, Sabharwal S. Outcome of colposcopy in women presenting with postcoital bleeding and negative or no cytology results of a 1-year audit. *J Obstet Gynaecol.* 2002; 22(3):299-301.

Jensen KE, Schmiedel S, Norrild B, Frederiksen K, Iftner T, Kjaer SK. Parity as a cofactor for high-grade cervical disease among women with persistent human papillomavirus infection: a 13-year follow-up. *Br J Cancer.* 2013; 108(1):234-9.

Kaplan KJ, Dainty LA, Dolinsky B, Rose GS and Carlson J: Prognosis and recurrence risk for patients with cervical squamous intraepithelial lesions diagnosed during pregnancy. *Cancer.* 2004; 102(4):228-32.

Kaneshiro BE, Acoba JD, Holzman J, Wachi K, Carney ME. Effect of delivery route on natural history of cervical dysplasia. *Am J Obstet Gynecol.* 2005; 192(5):1452-4.

Kaur J, Dey P, Saha SC, Rajwanshi A, Nijhawan R, Radhika S, Gupta N. Cervical cytology in patients with postmenopausal bleeding. *Diagn Cytopathol.* 2010; 38(7):496-8.

Kjellberg L, Hallmans G, Ahren AM, Johansson R, Bergman F, Wadell G, Angström T, Dillner J. Smoking, diet, pregnancy and oral contraceptive use as risk factors for cervical intra-epithelial neoplasia in relation to human papillomavirus infection. *Br J Cancer.* 2000; 82(7):1332-8.

Kotaniemi-Talonen L, Malila N, Anttila A, Nieminen P, Hakama M. Intensified screening among high risk women within the organised screening programme for cervical cancer in Finland. *Acta Oncol.* 2011; 50(1):106-11.

Kyrgiou M, Koliopoulos G, Martin-Hirsch P, Arbyn M, Prendiville W, Paraskevidis E. Obstetric outcomes after conservative treatment for intraepithelial or early invasive cervical lesions: systematic review and meta-analysis. *Lancet.* 2006; 367(9509):489-98.

Lee JM, Lee KB, Kim YT, Ryu HS, Kim YT, Cho CH, Namkoong SE, Lee KH, Choi HS, Kim KT. Cervical cancer associated with pregnancy: results of a multicenter retrospective Korean study (KGOG-1006). *Am J Obstet Gynecol.* 2008; 198(1):92.e1-6.

Louie KS, de Sanjose S, Diaz M. Early age at first sexual intercourse and early pregnancy are risk factors for cervical cancer in developing countries. *Br J Cancer.* 2009; 100(7):1191-7.

Lu DW, Pirog EC, Zhu X. Prevalence and typing of HPV DNA in atypical squamous cells in pregnant women. *Acta Cytol.* 2003; 47(6):1008–16.

Lowy DR, Schiller JT. Prophylactic human papillomavirus vaccines. *J Clin Invest.* 2006; 116(5):1167-73.

Marret H, Fauconnier A, Chabbert-Buffet N, Cravello L, Golfier F, Gondry J, Agostini A, Bazot M, Brailly-Tabard S, Brun JL, De Raucourt E, Gervaise A, Gompel A, Graesslin O, Huchon C, Lucot JP, Plu-Bureau G, Roman H, Fernandez H; CNGOF Collège National des Gynécologues et Obstétriciens Français. Clinical practice guidelines on menorrhagia: management of

abnormal uterine bleeding before menopause. *Eur J Obstet Gynecol Reprod Bio.* 2010; 152(2):133-7.

McIntyre-Seltman K, Lesnock JL. Cervical cancer screening in pregnancy. *Obstet Gynecol Clin North Am.* 2008; 35(4):645-58.

Ministério da Saúde. Diretrizes Brasileiras para Rastreamento do Câncer do Colo do Úterio. Rio de Janeiro: INCA; 2011.

Morice P, Uzan C, Gouy S, Verschraegen C, Haie-Meder C. Gynaecological cancers in pregnancy. *Lancet.* 2012; 379(9815):558-69.

Moscicki AB, Shiboski S, Hills NK, Powell KJ, Jay N, Hanson EN, Miller S, Canjura-Clayton KL, Farhat S, Broering JM, Darragh TM. Regression of low-grade squamous intra-epithelial lesions in young women. *Lancet.* 2004; 364(9446):1678-83.

Moscicki AB, Cox JT. Practice improvement in cervical screening and management (PICSM): symposium on management of cervical abnormalities in adolescents and young women. *J Low Genit Tract Dis.* 2010; 14(1):73-80.

Muller CY, Smith HO. Cervical neoplasia complicating pregnancy. *Obstet Gynecol Clin North Am.* 2005; 32(4):533-46.

Naylor B. The century for cytopathology. *Acta Cytol.* 2000; 44(5):709-25.

National Health Service Cervical Screening Programme. Colposcopy and programme management. Sheffield: NHSCP; 2010.

Onuma K, Saad RS, Kanbour-Shakir A, Kanbour AL, Dabbs DJ. Clinical implications of the diagnosis “atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion” in pregnant women. *Cancer*. 2006; 108(5):282-7.

Paavonen J. Human papillomavirus infection and the development of cervical cancer and related genital neoplasias. *Int J Infect Dis* 2007; 11(Suppl 2):S3-9.

Palle C, Bangsboll S, Andreasson B. Cervical intraepithelial neoplasia in pregnancy. *Acta Obstet Gynecol Scand*. 2000; 79(4):306-10.

Paraskevaidis E, Koliopoulos G, Kalantaridou S, Pappa L, Navrozoglou I, Zikopoulos K, Lolis DE. Management and evolution of cervical intraepithelial neoplasia during pregnancy and postpartum. *Eur J Obstet Gynecol Reprod Biol*. 2002; 104(1):67-9.

Plummer M, Peto J, Franceschi S. International Collaboration of Epidemiological Studies of Cervical Cancer. Time since first sexual intercourse and the risk of cervical cancer. *Int J Cancer*. 2012; 130(11):2638–44.

Popadiuk C, Stankiewicz A, Dickinson J, Pogany L, Miller AB, Onysko J. Invasive cervical cancer incidence and mortality among canadian women aged 15 to 29 and the impact of screening. *J Obstet Gynaecol Can*. 2012; 34(12):1167-76.

Ray P, Kaul V. Prevalence of high-grade squamous intraepithelial neoplasia (HiSIL) in symptomatic women referred to the colposcopy clinic with negative cytology. *Arch Gynecol Obstet*. 2008; 277(6):501-4.

Rodriguez AC, Schiffman M, Herrero R, Hildesheim A, Bratti C, Sherman ME, Solomon D, Guillén D, Alfaro M, Morales J, Hutchinson M, Katki H, Cheung L, Wacholder S, Burk RD. Longitudinal Study of Human Papillomavirus Persistence and Cervical Intraepithelial Neoplasia Grade 2/3: Critical Role of Duration of Infection. *J Natl Cancer Inst.* 2010; 102(5):315–324.

Ronco G, Pilutti S, Patriarca S, Montanari G, Ghiringhello B, Volante R, Giordano L, Zanetti R, Mancini E, Segnan N; Turin Cervical Screening Working Group. Impact of the introduction of organised screening for cervical cancer in Turin, Italy: cancer incidence by screening history 1992-98. *Br J Cancer.* 2005; 93(3):376-8.

Rosenthal AN, Panoskaltsis T, Smith T, Soutter WP. The frequency of significant pathology in women attending a general gynaecological service for postcoital bleeding. *BJOG.* 2001; 108(1):103-6.

Sanjosé S, Diaz M, Castellsagué X, Clifford G, Bruni L, Muñoz N, Bosch FX. Worldwide prevalence and genotype distribution of cervical human papillomavirus DNA in women with normal cytology: a meta-analysis. *Lancet Infect Dis.* 2007; 7(7):453-9.

Sasieni P, Adams J, Cuzick J. Benefit of cervical screening at different ages: evidence from the UK audit of screening histories. *Br J Cancer.* 2003; 89(1):88-93.

Saslow D, Solomon D, Lawson HW, Killackey M, Kulasingam SL, Cain J, Garcia FA, Moriarty AT, Waxman AG, Wilbur DC, Wentzensen N, Downs LS Jr, Spitzer M, Moscicki AB, Franco EL, Stoler MH, Schiffman M, Castle

PE, Myers ER; American Cancer Society; American Society for Colposcopy and Cervical Pathology; American Society for Clinical Pathology. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. *Am J Clin Pathol*. 2012; 137(4):516-42.

Schiffman M, Castle PE, Jeronimo J, Rodriguez AC, Wacholder S. Human papillomavirus and cervical cancer. *Lancet*. 2007; 370(9590):890-907.

See AT, Havenga S. Outcomes of women with postcoital bleeding. *Int J Gynaecol Obstet*. 2013; 120(1):88-9.

Selo-Ojeme DO, Dayoub N, Patel A, Metha M. A clinic-pathological study of postcoital bleeding. *Arch Gynecol Obstet*. 2004; 270(1):34-6.

Shapley M, Jordan K, Croft PR . An epidemiological survey of symptoms of menstrual loss in the community. *Br J Gen Pract*. 2004; 54(502):359–363.

Shapley M, Jordan J, Croft PR. A systematic review of postcoital bleeding and risk of cervical cancer. *Br J Gen Pract*. 2006; 56(527):453-60.

Siebers AG, Klinkhamer PJ, Grefte JM, Massuger LF, Vedder JE, Beijers-Broos A, Bulten J, Arbyn M. Comparison of liquid-based cytology with conventional cytology for detection of cervical cancer precursors: a randomized controlled trial. *JAMA*. 2009; 302(16):1757-64.

Sigurdsson K. Is a liquid-based cytology more sensitive than a conventional Pap smear? *Cytopathology*. 2013; 24(4):254-63.

Snijders PJ, Steenbergen RD, Heideman DA, Meijer CJ. HPV-mediated cervical carcinogenesis: concepts and clinical implications. *J Pathol.* 2006; 208(2):152-64.

Solomon D, Nayar R, eds. *The Bethesda system for reporting cervical/vaginal cytologic diagnoses: Definitions, criteria, and explanatory notes for terminology and specimen adequacy.* 2. ed. Rio de Janeiro: Revinter; 2005.

Spence AR, Goggin P, Franco EL. Process of care failures in invasive cervical cancer: systematic review and meta-analysis. *Prev Med.* 2007; 45(2-3):93-106.

Stonehocker J. Cervical Cancer Screening in Pregnancy. *Obstet Gynecol Clin North Am.* 2013; 40(2):269–282.

Tehrani A, Rezaii N, Mohit M, Eslami B, Arab M, Asgari Z. Evaluation of women presenting with postcoital bleeding by cytology and colposcopy. *Int J Gynaecol Obstet.* 2009; 105(1):18-20.

The 1988 Bethesda System for reporting cervical/vaginal cytological diagnoses. National Cancer Institute Workshop. *JAMA.* 1989; 262:931–4.

Traut HF, Papanicolaou GN. Cancer of the Uterus: The Vaginal Smear in Its Diagnosis. *Cal West Med.* 1943; 59(2):121-2.

Vaccarella S, Herrero R, Dai M, Snijders PJ, Meijer CJ, Thomas JO, Hoang Anh PT, Ferreccio C, Matos E, Posso H, de Sanjosé S, Shin HR, Sukvirach S, Lazcano-Ponce E, Ronco G, Rajkumar R, Qiao YL, Muñoz N, Franceschi S. Reproductive Factors, Oral Contraceptive Use, and Human Papillomavirus

Infection: Pooled Analysis of the IARC HPV Prevalence Surveys. *Cancer Epidemiol Biomarkers Prev.* 2006; 15(11):2148-53.

Vale DB, Westin MC, Zeferino LC. High-grade squamous intraepithelial lesion in women aged <30 years has a prevalence pattern resembling low-grade squamous intraepithelial lesion. *Cancer Cytopathol.* 2013; 121(10):576-81.

Van Calsteren K, Vergote I, Amant F. Cervical neoplasia during pregnancy: diagnosis, management and prognosis. *Best Pract Res Clin Obstet Gynaecol.* 2005; 19(4):611-30.

Van Doorn HC, Opmeer BC, Kooi GS, Ewing-Graham PC, Kruitwagen RF, Mol BW. Value of cervical cytology in diagnosing endometrial carcinoma in women with postmenopausal bleeding. *Acta Cytol.* 2009; 53(3):277-82.

Viikki M, Pukkala E, Hakama M. Bleeding symptoms and subsequent risk of gynecological and other cancers. *Acta Obstet Gynecol Scand.* 1998; 77(5):564-9.

Waggoner SE. Cervical cancer. *Lancet.* 2003; 361(9376):2217-25.

Warren JB, Gullett H, King VJ. Cervical cancer screening and updated Pap guidelines. *Prim Care.* 2009; 36(1):131-49.

Wiebe E, Denny L, Thomas G. Cancer of the cervix uteri. *International Journal of Gynecology & Obstetrics.* 2012; 119S2:S100–S109.

Williams JH, Carter SM, Rychetnick L. “Organised” cervical screening 45 years on: How consistent are organised screening practices? *Eur J Cancer.* 2014; 50(17):3029-38.

Wong HY, Loke AY, Chan NH. Risk factors for cervical abnormalities among Hong Kong Chinese women: a large-scale community-based cervical screening program. *J Womens Health (Larchmt)*. 2011; 20(1):53-9.

Wu YM, Wang T, He Y, Song F, Wang Y, Zhu L, Kong WM, Duan W, Zhang WY. Clinical management of cervical intraepithelial neoplasia in pregnant and postpartum women. *Arch Gynecol Obstet*. 2014; 289(5):1071-7.

Yang KY. Abnormal Pap Smear and Cervical Cancer in Pregnancy. *Clin Obstet Gynecol*. 2012; 55(3):838-48.

1.11. OBJETIVOS

1.11.1. Objetivo geral

Contribuir para a caracterização de fatores associados ao resultado de citologia cérvico-vaginal alterado para mulheres gestantes e para mulheres com informação clínica de sangramento genital.

1.11.2. Objetivos específicos

- Comparar a frequência de resultados de citologia cérvico-vaginal alterados em mulheres gestantes e não-gestantes estratificadas em grupos etários;
- Avaliar possível associação entre resultado de citologia cérvico-vaginal alterado e idade de início da atividade sexual para mulheres gestantes e não-gestantes;
- Avaliar possível associação entre resultado de citologia cérvico-vaginal alterado e intervalo entre exames para mulheres gestantes e não-gestantes;
- Comparar a qualidade do esfregaço (satisfatória, insatisfatória por excesso de hemácias, insatisfatória por outras causas) para mulheres com e sem informação clínica de sangramento genital estratificadas em dois grupos etários (até 50 anos x 50 anos ou mais);
- Comparar a frequência de resultados de citologia cérvico-vaginal alterados entre mulheres com e sem informação clínica de sangramento genital estratificadas em grupos etários.

Capítulo II: Artigos científicos

Artigo 1

Xavier-Júnior JC, Dufloth RM, do Vale DB, Tavares TA, Zeferino LC. High-grade squamous intraepithelial lesions in pregnant and non-pregnant women. Eur J Obstet Gynecol Reprod Biol. 2014; 175:103-6.

Artigo 2

Xavier-Júnior JCC, Vale DB, Vieira LFF, Zeferino LC, Dufloth RM. Pregnant and non-pregnant women have similar rates of high-grade squamous intraepithelial lesion.

Submetido ao International Journal of Gynecology & Obstetrics

Artigo 3

Xavier-Júnior JCC, Vale DB, Zeferino LC, Dufloth RM. Association between concurrent genital bleeding and cervical cancer, an observational analytical study

Submetido à Acta Obstetricia et Gynecologica Scandinavica



High-grade squamous intraepithelial lesions in pregnant and non-pregnant women



José Cândido C. Xavier-Júnior^a, Rozany M. Dufloth^{a,*}, Diama B. do Vale^b,
Thalita A. Tavares^a, Luiz C. Zeferino^b

^aUNESP – Universidade Estadual Paulista, Pathology Department, Botucatu, SP, Brazil

^bUNICAMP – Universidade Estadual de Campinas, Department of Obstetrics and Gynecology, Oncology Division, Campinas, SP, Brazil

ARTICLE INFO

Article history:

Received 19 October 2013

Received in revised form 6 December 2013

Accepted 12 January 2014

Keywords:

Papanicolaou smear

Pregnancy

Cervical cancer screening

Cervical intraepithelial neoplasia

Age

ABSTRACT

Objectives: To evaluate if the prevalence of cervical smear results varies between pregnant and non-pregnant women stratified by age group.

Study design: Observational analytical study with a total sample of 1,336,180 pregnant and non-pregnant women, aged between 20 and 34 years, who underwent cervical cancer screening in the Primary Health Care of the national health system in the area of Campinas in Brazil during the period of 2005–2009. The source is the information system for cervical cancer screening. Data collected on abnormal cervical smears were analyzed using the Chi-square test and Fisher's exact test and the magnitude of the association between pregnancy and high-grade squamous epithelial lesions was analyzed by odds ratio (OR) and estimated values with confidence intervals (CI) of 95%.

Results: 15,190 pregnant women and 395,961 non-pregnant women were analyzed and fulfilled the inclusion criteria. Regardless of age, no statistical differences were observed for high-grade squamous intraepithelial lesion prevalence (OR 0.90; CI 0.66–1.23). Taking into account the five-year age groups, however, low-grade squamous intraepithelial lesion was less prevalent in pregnant women aged 20–24 (OR 0.71; 0.54–0.95) and 25–29 years (OR 0.56; 0.35–0.89); also, atypical squamous cells of undetermined significance was more prevalent in non-pregnant women aged 25–29 years (OR 0.72; 0.54–0.97).

Conclusion: The study showed that the cytological prevalence of high-grade squamous intraepithelial lesion was similar in pregnant and non-pregnant women, regardless of age. The results indicate that there are no reasons for specific approaches to cervical cancer screening for pregnant women. The examination should be carried out only on pregnant women who have not been tested according to current recommendations.

© 2014 Elsevier Ireland Ltd. All rights reserved.

1. Introduction

Cervical cancer is the most preventable neoplasia and the cervical smear test continues to be the tool for early detection of precursor lesions [1,2]. High parity and young age at first full-term pregnancy have been described as risk factors for cervical cancer [3,4]. It is estimated that cervical cancer occurs at rates ranging from one to twelve cases per ten thousand pregnancies, setting it as the most frequently diagnosed malignancy in pregnancy [5–10].

The prevalence of abnormal precursor lesions is not uniform in all populations and may vary due to particularities of the studied groups [4–6,10–12].

Moreover, the incidence of HPV infection is higher in women aged 20–25 years, and the development of precursor lesions is associated with persistence of the infection [11–14]. Most pregnancies occur when women are aged between 18 and 35 years, which is the same age group that has the highest rates of the precursor lesions of cervical cancer [6]. Besides, there are recommendations in current literature that cervical smears are a component of routine pregnancy care, especially for women who had not been tested before becoming pregnant; establishing it as the only method for cancer screening performed during pregnancy [5–10].

Despite campaigns and the work of health teams, there is a high frequency of women who do not perform routine gynecological

* Corresponding author at: Department of Pathology, Botucatu Medical School, Paulista State University (UNESP), R. R. S. Rubião Júnior s/n, 18618-970 Botucatu, SP, Brazil. Tel.: +55 14 3811 6238; fax: +55 14 3815 2348.

E-mail address: rozany@fmb.unesp.br (R.M. Dufloth).

<http://dx.doi.org/10.1016/j.ejogrb.2014.01.018>

0301-2115/© 2014 Elsevier Ireland Ltd. All rights reserved.

Table 1
Frequency of cervical smear results in pregnant and non-pregnant women aged 20–34 years old.

Cervical smear diagnostic	Pregnant (n = 15 190)	Non-pregnant (n = 395 961)	OR ^f (CI ^g 95%)
ASCUS ^a	172 (1.1%)	5181 (1.3%)	0.86 (0.74–1.00)
LSIL ^b	80 (0.5%)	2655 (0.7%)	0.78 (0.62–0.98)
HSIL ^c + ISC ^d	42 + 0 (0.3%)	1198 + 13 (0.3%)	0.90 (0.66–1.23)
Negative ^e	14 896 (98.1%)	386,914 (97.7%)	1

$p > 0.060$ Fisher test.

^a ASCUS: atypical squamous cells of undetermined significance.

^b LSIL: low-grade squamous intraepithelial lesion.

^c HSIL: high-grade squamous intraepithelial lesion.

^d ISC: invasive squamous carcinomas.

^e Negative: negative for intraepithelial lesion or malignancy.

^f OR: odds ratio

^g CI: Confidence interval.

examinations. In this context, many women have their first gynecological examination when they are pregnant [5,6,10], and therefore more advanced lesions could be diagnosed than expected for their age. Moreover, It is known that during pregnancy the analysis of a cervical smear can present diagnostic difficulties, for example the presence of inflammatory and decidual cells that may be confused with atypical changes of undetermined significance [2,8–10].

In this context, this study presents a large sample size (total sample of 1,336,180) of pregnant and non-pregnant women attending the same clinics. There are few studies, as far as we know, that aim to report the rates of abnormal cervical smears in pregnant and non-pregnant women categorized into specific age groups.

2. Material and methods

This was an observational analytical study for assessment of the prevalence of cervical lesions in pregnant and non-pregnant women aged between 20 and 34 years from a population living in the Campinas metropolitan region, a densely populated urban area in south-east Brazil (State of São Paulo). The sample consisted of tests obtained from the Cytopathology Laboratory database of Dr. José Aristodemos Pinotti Women's Hospital, Universidade Estadual de Campinas (Unicamp), from January 2005 to December 2009 (5 years). This laboratory receives tests collected for cervical cancer screening purposes from patients in 70 municipalities of the Campinas region. This database did not include any tests conducted in private clinics. The vast majority of women managed by the public health system had no access to private medicine.

Therefore, patients included in this database had only a very slight chance of being screened by the private health system.

Physicians or nurse practitioners in primary health care collected material for cytology testing. The screening is opportunistic, so women were not invited for screening. No changes in delivery of the cervical cytology local services were observed over the five years of the study. The database contained patient identification, age and time since last cervical screening test. At the cytopathology laboratory, cytotechnologists performed routine evaluation and reading of the cervical smear tests. Cytopathologists reviewed suspicious cases. Thirty per cent of negative tests were randomly selected for quality control, carried out by senior cytotechnologists and cytopathologists.

The study excluded women who had had a previous cervical smear test within the last year, had a history of cervical cancer, or those that had been submitted to radiotherapy or chemotherapy. Incorrectly labeled tests and those classified as unsatisfactory or for purposes other than screening were also excluded. The results of cervical smears were reported by pathologists according to Solomon et al. [15], and were categorized as: negative for intraepithelial lesion or malignancy, atypical squamous cells of undetermined significance (ASCUS), low-grade squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion (HSIL), atypical glandular cells (AGC), atypical glandular cells suspicious for neoplasia and adenocarcinoma in situ, invasive squamous carcinomas (ISC) and invasive adenocarcinomas. Since the categories were based on the classification from the beginning of the 90s, a category of atypical squamous cells that cannot exclude HSIL (ASC-H) [16] was not considered. Therefore the following results were included in this study: negative for

Table 2
Cervical smear results in pregnant and non-pregnant women stratified by age-group.

Age-groups (years)		Cervical smear results				
		Negative ^a	ASCUS ^b	LSIL ^c	HSIL ^d	ISC ^e
20–24	Pregnant	6999 (97.7%)	99 (1.4%)	50 (0.7%)	17 (0.2%)	0 (0.0%)
	Non-pregnant	127,967 (97.2%)	2077 (1.5%)	1275 (1.0%)	389 (0.3%)	1 (0.0%)
	OR ^f (CI ^g 95%)	1	0.87 (0.70–1.06)	0.71 (0.54–0.95)	0.80 (0.49–1.29)	
25–29	Pregnant	4912 (98.4%)	48 (0.9%)	18 (0.4%)	16 (0.3%)	0 (0.0%)
	Non-pregnant	131,909 (97.7%)	1769 (1.4%)	862 (0.6%)	455 (0.3%)	4 (0.0%)
	OR ^f (CI ^g 95%)	1	0.72 (0.54–0.97)	0.56 (0.35–0.89)	0.93 (0.56–1.53)	
30–34	Pregnant	2985 (98.5%)	25 (0.8%)	12 (0.4%)	9 (0.3%)	0 (0.0%)
	Non-pregnant	127,038 (98.3%)	1335 (1.0%)	518 (0.4%)	354 (0.3%)	8 (0.0%)
	OR ^f (CI ^g 95%)	1	0.79 (0.53–1.19)	0.99 (0.55–1.75)	1.05 (0.54–2.04)	

^a Negative: negative for intraepithelial lesion or malignancy.

^b ASCUS: atypical squamous cells of undetermined significance.

^c LSIL: low-grade squamous intraepithelial lesion.

^d HSIL: high-grade squamous intraepithelial lesion.

^e ISC: invasive squamous carcinomas.

^f OR: odds ratio.

^g CI: confidence interval.

intraepithelial lesion or malignancy, ASC-US, LSIL, HSIL or invasive squamous carcinoma. From a total of 1,336,180 tests performed in the period 2005–2009 (after applying the inclusion and exclusion criteria), the study sample consisted of 15,190 pregnant and 395,961 non-pregnant women.

The analyzed patients were stratified into three age groups (20–24 years, 25–29 years and 30–34 years old), as reported at the examination. The association of abnormal cervical smears with data collected was analyzed using the Chi-square test and Fisher's exact test and the measure of the magnitude of the association was analyzed by odds ratio (OR) estimated values with 95% confidence intervals (CI). Data were presented in absolute (*n*) and relative frequencies (%) to assess the association between diagnostic categories. The significance level was 5% and the software used for the statistical analysis was SAS, version 2.9.

3. Results

Considering all the women regardless of age-group, the prevalence rate of LSIL was lower for pregnant women (OR 0.78; CI 0.62–0.98), but the prevalence rate of HSIL + ISC was similar for both groups (OR 0.90; 0.66–1.23). For ASC-US, the prevalence rate was also lower for pregnant women with borderline significance (OR 0.86; 0.74–1.00) (Table 1).

Considering the age-groups, the prevalence rates of LSIL were lower for pregnant women in the age-groups 20–24 (OR 0.71; 0.54–0.95) and 25–29 years (OR 0.56; 0.35–0.89), but were similar for those in the age-group 30–34 years (OR 0.99; 0.55–1.75). The prevalence rates of ASCU-US were lower for pregnant women in the age-group 25–29 years (OR 0.72; 0.54–0.97), but were similar for those in the age-group 20–24 (OR 0.87; 0.70–1.06) and 30–34 years (OR 0.79; 0.53–1.19). The prevalence rates of HSIL were similar for pregnant and non-pregnant women in the three age-groups analyzed (Table 2).

4. Comments

This study shows that the cytological prevalence of HSIL is similar in pregnant and non-pregnant women, regardless of age. Moreover, it shows that the prevalence of LSIL and ASC-US is lower in pregnant women aged 20–24 years. These findings are not opposed to the understanding that high parity and young age at first full-term pregnancy have been described as risk factors for cervical cancer [3,4]. Until recently it has been unclear whether these variables were also associated with increased risk of acquisition and persistence of human papillomavirus (HPV) infection. Recent studies suggested that these factors might be involved in the transition from HPV infection to neoplastic cervical lesions during carcinogenesis [1,4,7,9,12,13].

Considering that the true precursor lesion is CIN 3 or HSIL at cytological diagnosis [3,11–14,17], and considering that the women included in this study were younger than 35 years old, the expected rate of true precursor lesions should be lower, as well as the incidence of cervical cancer. Currently, LSIL has been considered as a morphological expression of transient HPV infection and not a precursor lesion and, therefore, it could be considered a parameter for making some inferences on HPV acquisition [1,4,7,13,17]. Following this understanding, the findings of this study suggested that the non-pregnant women were more likely to have HPV infection as the LSIL prevalence in non-pregnant women was higher than in pregnant women, which could be applied only for this population without any obvious explanation. In the literature the rates of abnormal cervical smears during pregnancy are widely variable, but there is some convergence to the agreement that these rates are similar between

pregnant and non-pregnant women [3,8–10] as are the rates of HPV infection [2,9].

Moreover, this study showed no findings suggesting that in the presence of clinical information about pregnancy the cytological analysis could be adversely affected, but the authors believe that communication between clinicians and cytopathologists is relevant for more appropriate cytological analysis [9].

This study did not include previous screening as a variable because these data were not available, but some consideration of this may be necessary. Cytological cervical screening is effective in reducing the HSIL prevalence rate mainly in women over 30 years old. The HSIL prevalence observed for pregnant and non-pregnant women was similar, suggesting that the screening history of the women should not differ significantly between these two groups. Another consideration is that there is no information about the corresponding histological diagnoses for these women, although these two weak points could be balanced by the large sample analyzed.

In conclusion, the findings of this study indicate that there are no reasons for specific approaches to cervical cancer screening for pregnant women, and compulsory cervical smear tests in pre-natal care should be abandoned [2]. Nevertheless, during pre-natal care there is an opportunity to carry out a cervical smear test for women who have not been tested in the last three years or according to current recommendations [1,2].

Conflict of interest

None.

Funding

There are no funding sources.

Acknowledgements

The team of the Center for Integrated Health of Women, State University of Campinas, São Paulo – Brazil (CAISM-Unicamp/Brazil).

References

- [1] Saslow D, Solomon D, Lawson HW, et al. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. *Am J Clin Pathol* 2012;137:516–42.
- [2] Stonehocker J. Cervical cancer screening in pregnancy. *Obstet Gynecol Clin North Am* 2013;40:269–82.
- [3] Jensen KE, Schmiedel S, Norrild B, Frederiksen K, Iftner T, Kjaer SK. Parity as a cofactor for high-grade cervical disease among women with persistent human papillomavirus infection: a 13-year follow-up. *Br J Cancer* 2013;108:234–9.
- [4] Vaccarella S, Herrero R, Dai M, et al. Reproductive factors, oral contraceptive use, and human papillomavirus infection: pooled analysis of the IARC HPV prevalence surveys. *Cancer Epidemiol Biomarkers Prev* 2006;15:2148–53.
- [5] Coleman CA. Evaluation and management of abnormal cervical cytology during pregnancy. *Clin Obstet Gynecol* 2013;56:51–4.
- [6] Frega A, Scirpa P, Corosu R, et al. Clinical management and follow-up of squamous intraepithelial cervical lesions during pregnancy and postpartum. *Anticancer Res* 2007;27(4C):2743–6.
- [7] Govindappagari S, Schiavone MB, Wright JD. Cervical neoplasia. *Clin Obstet Gynecol* 2011;54:528–36.
- [8] Morice P, Uzan C, Gouy S, Verschraegen C, Haie-Meder C. Gynaecological cancers in pregnancy. *Lancet* 2012;379:558–69.
- [9] Muller CY, Smith HO. Cervical neoplasia complicating pregnancy. *Obstet Gynecol Clin North Am* 2005;32:533–46.
- [10] Yang KY. Abnormal Pap smear and cervical cancer in pregnancy. *Clin Obstet Gynecol* 2012;55:838–48.
- [11] Bano F, Kolhe S, Zamblera D, et al. Cervical screening in under 25s: a high-risk young population. *Eur J Obstet Gynecol Reprod Biol* 2008;139:86–9.
- [12] Bosch FX, de Sanjosé S. The epidemiology of human papillomavirus infection and cervical cancer. *Dis Markers* 2007;23:213–27.
- [13] Lowy DR, Schiller JT. Prophylactic human papillomavirus vaccines. *J Clin Invest* 2006;116:1167–73.

- [14] Snijders PJ, Steenberg RD, Heideman DA, Meijer CJ. HPV-mediated cervical carcinogenesis: concepts and clinical implications. *J Pathol* 2006;208: 152–64.
- [15] Solomon D, Nayar R. Sistema Bethesda para Citopatologia Cervicovaginal – Definições, Critérios e Notas Explicativas. 2nd ed. Rio de Janeiro: Revinter; 2005.
- [16] National Cancer Institute Workshop. The 1988. Bethesda System for reporting cervical/vaginal cytologic diagnoses. Bethesda: National Institutes of Health; 1989.
- [17] Vale DB, Westin MC, Zeferino LC. High-grade squamous intraepithelial lesion in women aged <30 years has a prevalence pattern resembling low-grade squamous intraepithelial lesion. *Cancer Cytopathol* 2013;121:576–81.

Title: Pregnant and non-pregnant women have similar prevalence of high-grade lesions regardless age, onset of sexual intercourse and screening history

Authors: José Cândido C. Xavier-Júnior, MD ^a; Diama B. Vale, MD, PhD ^b; Luiz Fernando Fonseca Vieira, MS ^a; Marcelo Tavares de Lima ^b, Luiz Carlos Zeferino, MD, PhD ^b; Rozany M. Dufloth, MD, PhD ^a

a- Pathology Department, Paulista State University (UNESP), Botucatu, Brazil

b- Department of Gynecology and Obstetrics, Campinas State University (UNICAMP), Campinas, Brazil

TYPE OF ARTICLE: Clinical Article

DISCLOSURE STATEMENT

Conflict of interest: none

There are no funding sources

Full Address:

Rozany Mucha Dufloth, MD, PhD
Department of Pathology
Botucatu Medical School
Paulista State University (UNESP)
Rubião Júnior s/n
18618-970. Botucatu – SP
Brazil
Telephone: + 55 (14) 3811-6238
Fax: + 55 (14) 38152348
Email: rozany@fmb.unesp.br

Synopsis

Regardless of age, the time since last Pap smear, age at first sexual intercourse, there is no difference between pregnant and non-pregnant women regarding HSIL

Key words: Pregnancy, Cervical Cancer Screening, Pap Smear, Cervical Intraepithelial Neoplasia, Age, First Sexual Intercourse, Sexual Behaviour.

Word count of the main text: 2484

Abstract:

Objective: To compare the prevalence of cytological results among pregnant and non-pregnant women and to assess the association with screening age, interval since the last screening and age of first sexual intercourse.

Study design: Observational analytical study to assess cytological results of women aged between 18 and 34 in the period 2000-2009, from the Campinas region, Brazil, who had not had cytological screening in a period of less than one year and women with no previous diagnosis of precursor lesions or cervical cancer. The analysis included 37,568 examinations on pregnant women and 861,353 examinations on non-pregnant women. Multinomial logistic regression was held for every age group and included: being pregnant, age of first sexual intercourse and interval since the last cervical cytology, taking high-grade squamous intraepithelial lesion (HSIL) as the end result.

Results: Pregnant and non-pregnant women showed similar prevalence of HSIL (0.4%). Regarding HSIL cytological results, the logistic regression showed no statistically significant differences between pregnant and non-pregnant women, taking into account age at screening, age of first sexual intercourse and interval since last screening exam for four age-groups of woman.

Conclusion: There is no reason to perform mandatory cervical cytology on pregnant women and, therefore, they may follow current protocols for non-pregnant women.

Introduction:

Due to the weakness of screening programs in developing countries, cervical cancer continues to have high incidence rates and it is one of the leading causes of death among women [1-3].

Reducing the incidence and mortality of carcinoma is consequent of screening exams which is dependent on the age of the women, the quality of the service and coverage of programs [2,4,5].

The average time for persistent HPV infections to progress to carcinoma of the cervix is 12-15 years. Since most infections healed spontaneously, and the development of cancer from the HPV infection has been a rare complication, the possibility of viral carcinogenesis has been discussed as a multifactorial process [3,6].

Pregnancy is one time in which women perform screening for cervical carcinoma [7,8]. The age group between 18 and 35 years corresponds to the age with highest concentration of pregnancies as well as the highest rates of HPV infection and precursor lesions [9]. Furthermore, it is emphasized that women under 30 years of age should have screening for cervical cancer exclusively through cytology examinations [5,8]. Thus, since carcinoma of the cervix has been a frequently diagnosed malignancy in pregnancy [8 -10], it would be valuable to see if the prevalence of precursor lesions was similar between pregnant women and non-pregnant women.

Currently, it is almost a consensus that the three-year interval for cytological exam is sufficient [5]. A significant number of recommendations indicate the beginning of screening of women aged between 20 and 25 years, but the recommendations vary from 18 to 30 years [1,4,5,11]. The exclusion of

very young women avoids unnecessary anxiety and decreases the performance of diagnostic and therapeutic procedures that can cause obstetric and neonatal morbidity [12]. However, there is a lack of objective information as to the risk of neoplastic changes of the cervix in pregnant women maintaining the same pattern as non-pregnant women. This study aims to compare the prevalence of cytology results among pregnant and non-pregnant women and to evaluate the association between age, time since last Pap smear and age of first sexual intercourse with the cytology result.

Materials and method:

This was an observational analytical study to assess the prevalence of cervical cancer screening cytological results in pregnant and non-pregnant women aged between 18 and 34 years. All women were in primary care of the public health system of the Campinas area - Brazil, from January 2000 to December 2009 (ten years). All exams were analysed at the Laboratory of Cytopathology of the Women's Hospital, State University of Campinas (Unicamp), Campinas – Brazil. This laboratory has a very experienced, professional team and has received examinations collected from patients originating from almost 70 cities in the Campinas region. The study included cytological examinations from women who had no screening examinations in a period less than one year, no previous diagnosis of precursor lesions or cervical cancer and whose age was known as well as age of first sexual intercourse. Examinations incorrectly labelled, classified as unsatisfactory or with purposes other than screening were excluded. Institutional Review Board (IRB) approval was obtained from Unicamp (No. 375/2010). The analyses were retrospective,

the anonymity of the women was preserved and, therefore, the IRB granted a waiver for the requirement to obtain a signed consent form.

The following cytological results were included in the analyses: negative for intraepithelial lesion or malignancy, atypical squamous cells of undetermined significance (ASCUS), low-grade squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion (HSIL). Women's data were collected during the gynaecological examination in a specific form that contains identification, age, age at first sexual intercourse, interval since last screening exam; the cytological results were added later, in the laboratory. All data were registered in the information system of Laboratory of Cytopathology that was constructed for screening management and for quality assessment purposes. At the laboratory, the cytotechnologists analysed the slides, the pathologists reviewed all suspicious or positive results and 30% of negative exams, according to internal quality control. The results of cervical cytology have been reported according to the Bethesda system [13,14]. From a total of 2,505,154 women, 37,568 pregnant and 861,353 non-pregnant women were analysed after applying the inclusion and exclusion criteria.

For statistical analysis, pregnant and non-pregnant women were stratified in four age groups (less than 21 years, 21-24 years, 25-29 years and 30-34 years). To analyse the relationship with cytological result, age at first sexual intercourse was considered as a continuous numeric variable and interval since the last screening examination was categorized into six categories: first exam, one year, two years, three years, four years and five years or more.

The descriptive data and the distribution of the cytological results according to age groups for pregnant and non-pregnant women were presented

as absolute (n) and relative (%) numbers. Using SAS software, version 2.9., multinomial logistic regression was held for every age group, taking HSIL as an end point. The independent variables were: pregnant, age of first sexual intercourse and interval since the last screening examination. The odds ratio (OR) and confidence intervals of 95% were calculated for logistic regression analyses. It was considered a risk factor when OR was greater than one and protective factor when less than one, as the value one was not included in the confidence intervals.

Results:

A total of 898,921 women with a mean age of 26 years and age of first sexual intercourse between 13 and 26 years were analysed, with 4.2% corresponding to pregnant women and 95.8% to non-pregnant women. The cytological results were negative for intraepithelial lesion or malignancy in 97.6% of cases, ASCUS occurred in 1.2%, LSIL in 0.8%, and HSIL exhibited prevalence of 0.4%. Women's screening history showed that 12.7% were having their first screening examination, 49.3% had had one a year before and only 3.4% had last screening examination with an interval of five years or more .

Considering the whole population studied, pregnant and non-pregnant women showed the same frequency of HSIL (0.4%). When stratified into four age groups; a frequency of 0.4% for non-pregnant women was observed from 18 to 29 years and 0.3% for women from 30 to 34 years. For pregnant women the higher frequency of HSIL was in the age group of 25-29 years (0.5%) while the other age-groups had the same frequency (0.3%). For pregnant and non-pregnant women was observed decrease of the ASCUS and LSIL rates with the

increase of age while negative results showed increase and HSIL rates were maintained (Table 1).

After application of the multinomial logistic regression model, it was found that, independent of age, the interval since the last screening exam and age of first sexual intercourse, that there was no statistically significant differences between pregnant and non-pregnant women regarding HSIL (younger than 21 years: OR 1.1, CI 0.8 - 1.6 / 21 to 24 years: OR 1.3, CI 0.9 - 1.8 / 25 to 29 years: OR 0.9, CI 0.7 - 1.127 / 30 to 34 years: OR 1.0, CI 0.6 - 1.5). Furthermore, it was found that, regardless of age, age of sexual intercourse was a protective factor for HSIL: the older the subject was at first sexual intercourse, the lower the chance of cytological result of HSIL (younger than 21 years: OR 0.9, CI 0.8 – 0.9/ 21 to 24 years: OR 0.9, CI 0.8 – 0.9/ 25 to 29 years: OR OR 0.9, CI 0.8 – 0.9/ 30 to 34 years: OR 0.9, CI 0.8 – 0.9) (Table 2).

Regarding the time since the last screening examination, for women younger than 21 years there was no association between the examination interval and the prevalence of HSIL. For women aged between 21 to 24 years, the intervals between cytology examinations equal to 1 year, 2 years and 3 years versus five years or more, were considered protective factors for HSIL (1 year vs 5 years or more OR 0.5, CI 0.3 to 0.766 / 2 years vs. 5 years or more OR 0.6, CI 0.4 to 0.8 / 3 years vs 5 years or more OR 0.6, CI 0.4 to 0.9). There was no difference between first exam (OR 0.7, CI 0.5 – 1.1) and four years of interval (OR 0.8, CI 0.5 – 1.2) when compared to five years or more for HSIL. For women that were 25 to 29 years old, considering the first examination in relation to an interval of 5 years or more, the first exam was a risk factor for HSIL (OR 1.4, CI 1.0 to 1.9); intervals of one year (OR 0.5, CI 1.0 – 1.9) and

two years (OR 0.7, CI 0.5 – 0.9) when considered, in relation to 5 years or more, as protective factors, while 3 years (OR 0.9, CI 0.6 – 1.2) or four years (OR 1.0, CI 0.7 – 1.4) of interval had no statistical association. Women aged between 30 and 34 years old, with the exception of first examination (OR 1.3, IC 0.9 – 1.9), all intervals when compared with 5 years of interval were considered protective factors (1 year vs 5 years or more OR 0.4, CI 0.3 – 0.5 / 2 years vs 5 years or more OR 0.6, CI 0.5 – 0.8 / 3 years vs 5 years or more OR 0.6, CI 0.5 – 0.9 / 4 years vs 5 years or more OR 0.5, CI 0.4 – 0.8) (Table 2).

Discussion:

This study demonstrated that regardless of age, the interval since the last screening exam and age of first sexual intercourse, there is no difference in the prevalence of HSIL among pregnant and non-pregnant women. In this context, it should be noted that the accuracy of the examination of cytological examination does not vary with gestation [10]. Moreover, rates of HSIL are not different between pregnant and non-pregnant women [9,15], even when stratified by risk factors (age, time interval between examinations and age of first sexual intercourse); whereas, rates of HPV infection are similar between the two groups of women analysed [8,9].

There were discussions about the influence of pregnancy and childbirth on the natural history of cervical cancer [9,10,15,16] and the prevalence of HPV infection,[17] suggesting that pregnancy cannot configure a risk factor for abnormal cytology result. In addition, Lee *et al* [9] showed no difference in overall survival between pregnant and non-pregnant women with early stage carcinoma of the cervix.

Currently, we question the recommendation that all pregnant women should undergo routine cytological exam in their prenatal care [7,8]. The American College of Obstetricians and Gynaecologists (ACOG) suggest that pregnant women over 30 years who do not have a history of dysplasia, immunodeficiency or intrauterine exposure to diethylstilbestrol and present three or more previous cytological results without abnormalities, can be submitted for a post-partum interval between examinations of three-years, the same as the existing protocols for non-pregnant women [7]. Data from this study confirmed a previous work statement of our research group [18] that indicates no significant difference between pregnant and non-pregnant women regardless of age and HSIL; suggesting, therefore, that pregnant women should not be subjected to compulsory cytology examinations.

Furthermore, this study demonstrated that young age of first sexual intercourse is associated with increased prevalence of HSIL. Noteworthy, is the age of first sexual intercourse as an important risk factor for cervical cancer [19, 20], in a logarithmic, non-linear relationship [20]. Even when stratified by other demographic risk factors such as educational level, number of sexual partners, parity or smoking; the age of onset of sexual activity remains related to cervical carcinoma [21]. For this, one should take into account that women who became sexually active at a young age are also associated with higher rates of HPV infection [19].

However, Jensen et al. [16] did not identify an association between age of first sexual intercourse and cervical intraepithelial neoplasia grade III (CIN 3). In addition Vaccarella et al. [22] did not observe an association between the onset of sexual activity after 25 years and decreased risk of HPV infection

compared to women who initiated sexual activity before 20 years. In this context, it is suggested that different factors of HPV infection may play a role in increasing the risk or duration of infection and progression of HPV infection to cervical carcinoma [22], since cervical cancer at younger ages (below 35 years) is associated with young age of first sexual intercourse [21].

There is no uniformity among American [5,8,11], Canadian [4] and European countries [1] recommendations about the age of onset of screening examinations for cervical carcinoma and it is proposed that the number of women with CIN 3 before 25 years of age is not insignificant [23]. Data from this study showed no difference between the intervals of examination for women under 21 years. Since that age-group is out of standard international protocols for cervical cancer screening [1,4,5,11], this find might be understood as another reason not to recommend the Pap smear for that population.

The screening programs for women aged between 21 and 24 years have controversial recommendations [1,4,5,11]. The United States Preventive Services Task Force, the ACOG and the American Cancer Society recommend the screening with cytology alone every three years [5,11] while some European countries and the Canadian protocol recommend screening for women aged from 25 years. This study identified intervals from one, two or three years as protection factor for women in that age-group which is in agreement with the American recommendations.

For women between 25 and 29 years, routine screening with cytology alone every three years is recommended [1,5]. Nevertheless, in this study, three years interval had no protection effect which can be analysed as one possible feature of the studied population or a sign that smaller intervals like

one and two years should be considered for that age-group. In addition, the first examination was identified as a risk factor for HSIL for women between 25 and 29 years, an argument against the later onset of screening. A risk factor was identified for women between 30 and 34 years-old who had a five year interval between examinations and this result discourages the use of five-year intervals between examinations, in accordance with international protocols [4,5].

The limits of this study include the lack of previous and sequential cytology data and cytological results were not confirmed on histology, points that exceed the goals of the study. Moreover, the relevant sample size (2,505,154 women) is highlighted as a strong point of this study.

In conclusion, the results of this study indicated that there are no reasons to perform mandatory Pap smear in pregnant women. Pregnant women may follow current protocols for non-pregnant women. Furthermore, we identified an association between HSIL and first cytology exam for women between 25 and 29 years; and HSIL and young age of first sexual intercourse for all age groups analyzed. In this context, from the data presented, it is recommended that the onset of examinations is from 25 years, discouraging the five year interval between examinations and reaffirming that pregnant women should not necessarily be submitted to Pap smear routinely during prenatal care.

Acknowledgements:

The team at the Center for Integrated Health of Women, State University of Campinas, São Paulo - Brazil (CAISM-Unicamp / Brazil)

Conflict of interest:

None

Referências:

1. Anttila A, von Karsa L, Aasmaa A, Fender M, Patnick J, Rebolj M, et al. Cervical cancer screening policies and coverage in Europe. *Eur J Cancer* 2009;45(15):2649-58.
2. Denny L. Cytological screening for cervical cancer prevention. *Best Pract Res Clin Obstet Gynaecol* 2012;26(2):189–96.
3. Lowy DR, Schiller JT. Prophylactic human papillomavirus vaccines. *J Clin Invest* 2006;116(5):1167-73.
4. Canadian Task Force on Preventive Health Care, Dickinson J, Tsakonas E *et al.* Recommendations on screening for cervical cancer. *CMAJ* 2013; 8;185(1):35-45.
5. Saslow D, Solomon D, Lawson HW, Killackey M, Kulasingam SL, Cain J, et al. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. *Am J Clin Pathol* 2012;137(4):516-42.
6. Snijders PJ, Steenbergen RD, Heideman DA, Meijer CJ. HPV-mediated cervical carcinogenesis: concepts and clinical implications. *J Pathol* 2006;208(2):152-64.
7. Hunter MI, Monk BJ, Tewari KS. Cervical neoplasia in pregnancy. Part 1: screening and management of preinvasive disease. *Am J Obstet Gynecol* 2008;199(1):3-9.
8. Kaplan KJ, Dainty LA, Dolinsky B, Rose GS, Carlson J, McHale M, et al. Prognosis and Recurrence Risk for Patients with Cervical Squamous

- Intraepithelial Lesions Diagnosed during Pregnancy. *Cancer Cytopathol* 2004;102(4):228-32.
9. Lee JM, Lee KB, Kim YT, Ryu HS, Kim YT, Cho CH, et al. Cervical cancer associated with pregnancy: results of a multicenter retrospective Korean study (KGOG-1006). *Am J Obstet Gynecol* 2008;198(1):92.e1-6.
 10. Stonehocker J. Cervical Cancer Screening in Pregnancy. *Obstet Gynecol Clin North Am.* 2013;40(2):269–282.
 11. Warren JB, Gullett H, King VJ. Cervical cancer screening and updated Pap guidelines. *Prim Care* 2009;36(1):131-49.
 12. Sasieni P, Adams J, Cuzick J. Benefit of cervical screening at different ages: evidence from the UK audit of screening histories. *Br J Cancer.* 2003;89(1):88-93.
 13. The 1988 Bethesda System for reporting cervical/vaginal cytological diagnoses. National Cancer Institute Workshop. *JAMA.* 1989;262:931–4.
 14. Solomon D, Nayar R, eds. The Bethesda system for reporting cervical/vaginal cytologic diagnoses: Definitions, criteria, and explanatory notes for terminology and specimen adequacy.. 2. ed. Rio de Janeiro: Revinter; 2005.
 15. Fader AN, Alward EK, Niederhauser A, Chirico C, Lesnock JL, Zwiesler DJ, et al. Cervical dysplasia in pregnancy: a multi-institutional evaluation. *Am J Obstet Gynecol.* 2010;203(2):113.e1-6.

16. Jensen KE, Schmiedel S, Norrild B, Frederiksen K, Iftner T, Kjaer SK. Parity as a cofactor for high-grade cervical disease among women with persistent human papillomavirus infection: a 13-year follow-up. *Br J Cancer*. 2013;108(1):234-9.
17. Rodríguez AC, Schiffman M, Herrero R, Hildesheim A, Bratti C, Sherman ME, et al. Longitudinal Study of Human Papillomavirus Persistence and Cervical Intraepithelial Neoplasia Grade 2/3: Critical Role of Duration of Infection. *J Natl Cancer Inst* 2010;102(5):315–324.
18. Xavier-Júnior JC, Dufloth RM, do Vale DB, Tavares TA, Zeferino LC. High-grade squamous intraepithelial lesions in pregnant and non-pregnant women. *Eur J Obstet Gynecol Reprod Biol*. 2014;175:103-6.
19. Louie KS, de Sanjose S, Diaz M. Early age at first sexual intercourse and early pregnancy are risk factors for cervical cancer in developing countries. *Br J Cancer*. 2009;100(7):1191-7.
20. Plummer M, Peto J, Franceschi S. International Collaboration of Epidemiological Studies of Cervical Cancer. Time since first sexual intercourse and the risk of cervical cancer. *Int J Cancer* 2012;130(11):2638–44.
21. Edelstein ZR, Madeleine MM, Hughes JP, Johnson LG, Schwartz SM, Galloway DA, et al. Age of diagnosis of squamous cell cervical carcinoma and early sexual experience. *Cancer Epidemiol Biomarkers Prev*. 2009;18(4):1070-6.

22. Vaccarella S, Herrero R, Dai M, Snijders PJ, Meijer CJ, Thomas JO, et al. Reproductive Factors, Oral Contraceptive Use, and Human Papillomavirus Infection: Pooled Analysis of the IARC HPV Prevalence Surveys. *Cancer Epidemiol Biomarkers Prev.* 2006;15(11):2148-53.
23. Bano F, Kolhe S, Zamblera D, Jolaoso A, Folayan O, Page L, et al. Cervical screening in under 25s: a high-risk young population. *Eur J Obstet Gynecol Reprod Biol.* 2008; 139(1):86-9.
24. Popadiuk C, Stankiewicz A, Dickinson J, Pogany L, Miller AB, Onysko J. Invasive cervical cancer incidence and mortality among canadian women aged 15 to 29 and the impact of screening. *J Obstet Gynaecol Can.* 2012;34(12):1167-76.
25. Castanon A, Leung VM, Landy R, Lim AW, Sasieni P. Characteristics and screening history of women diagnosed with cervical cancer aged 20-29 years. *Br J Cancer.* 2013;109(1):35-41.

Table 1: Prevalence of cytological results for pregnant women and non-pregnant women stratified by age groups.

	Age	Cytological Results				Total
		Negative ^a n (%)	ASCUS ^b n (%)	LSIL ^c n (%)	HSIL ^d n (%)	
Non-pregnant	Less than 21 years old	132062 (96.7%)	2129 (1,6%)	1922 (1.4%)	485 (0.4%)	136598
	21-24 years old	206483 (97.3%)	2960 (1,4%)	2045 (1.0%)	824(0.4%)	212312
	25-29 years old	255690 (97.8%)	2992 (1,1%)	1709 (0.7%)	972 (0.4%)	261363
	30 years old or more	246829 (98.3%)	2409 (1,0%)	1051 (0.4%)	791 (0.3%)	251080
	Total	841064 (97.6%)	10490 (1.2%)	6727 (0.8)	3072 (0.4%)	861353
Pregnant	Less than 21 years old	9792 (97.3%)	129 (1.3%)	112 (1.1%)	33 (0.3%)	10066
	21-24 years old	11148 (97.5%)	141 (1.2%)	103 (0.9%)	36 (0.3%)	11428
	25-29 years old	9.798 (98.1%)	90 (0.9%)	57 (0.6%)	45 (0.5%)	9990
	30 years old or more	5.994 (98.5%)	45 (0.7%)	24 (0.4%)	21 (0.3%)	6084
	Total	36732 (97.8%)	405 (1.0%)	296 (0.8%)	135 (0.4%)	37568

a: Negative: negative for intraepithelial lesion or malignancy

b: ASCUS: atypical squamous cells of undetermined significance

c: LSIL: low-grade squamous intraepithelial lesion

d: HSIL: high-grade squamous intraepithelial lesion

Table 2: High Grade Squamous Intraepithelial Lesion prevalence in pregnant women and associated factors: logistic regression analysis

Age	Associated factors	OR^a	(CI^b 95%)	
Less than 21 years old	Non-pregnant	1.1 ^d	0.8	1.6
	First exam vs 5 years or more	0.7 ^d	0.3	1.5
	1 year vs 5 years or more	0.5 ^d	0.2	1.2
	2 years vs 5 years or more	0.6 ^d	0.3	1.4
	3 years vs 5 years or more	0.6 ^d	0.2	1.4
	4 years vs 5 yeras or more	1.0 ^d	0.4	2.7
	Age of first sexual intercourse ^c	0.9	0.8	0.9
21 to 24 years old	Non-pregnant	1.3 ^d	0.9	1.8
	First exam vs 5 years or more	0.7 ^d	0.5	1.1
	1 year vs 5 years or more	0.5	0.3	0.7
	2 years vs 5 years or more	0.6	0.4	0.8
	3 years vs 5 years or more	0.6	0.4	0.9
	4 years vs 5 years or more	0.8 ^d	0.5	1.2
	Age of first sexual intercourse ^c	0.9	0.8	0.9
25 to 29 years old	Non-pregnant	0.9 ^d	0.7	1.2
	First exam vs 5 years or more	1.4	1.0	1.9
	1 year vs 5 years or more	0.5	0.4	0.7
	2 years vs 5 years or more	0.7	0.5	0.9
	3 years vs 5 years or more	0.9 ^d	0.6	1.2
	4 years vs 5 years or more	1.0 ^d	0.7	1.4
	Age of first sexual intercourse ^c	0.9	0.8	0.9
30 years old or more	Non-pregnant	1.0 ^d	0.6	1.5
	First exam vs 5 years or more	1.3 ^d	0.9	1.9
	1 year vs 5 years or more	0.4	0.3	0.5
	2 years vs 5 years or more	0.6	0.5	0.8
	3 years vs 5 years or more	0.6	0.5	0.9
	4 years vs 5 years or more	0.5	0.4	0.8
	Age of first sexual intercourse ^c	0.9	0.8	0.9

a: Odds Ratio

b: Confidence Interval

c: Age of first sexual intercourse: the older the patient at onset of sexual activity the lower the chance of them having a cytology result of HSIL

d: Statistically not significant (alpha=0,05)

Title: Association between concurrent genital bleeding and cervical cancer, an observational analytical study

Running title: Genital bleeding and cervical cancer

Authors: José Cândido C. Xavier-Júnior, MD¹; Diama B. Vale, MD, PhD²; Luiz Carlos Zeferino, MD, PhD²; Rozany M. Dufloth, MD, PhD¹

- 1) Pathology Department, Paulista State University (UNESP), Botucatu, Brazil
- 2) Department of Gynaecology and Obstetrics, Campinas State University (UNICAMP), Campinas, Brazil

Rozany Mucha Dufloth, MD
Department of Pathology
Botucatu Medical School
Paulista State University (UNESP)
Rubião Júnior s/n
18618-970. Botucatu – SP
Brazil
Telephone: + 55 (14) 3811-6238
Email: rozany@fmb.unesp.br

DISCLOSURE STATEMENT

Conflict of interest: none

Abstract:

This is an observational analytical study where it was evaluated whether the prevalence of cervical smear results is different in women with and without clinical information about concurrent genital bleeding. The sample consisted of 2 324 836 smears, of these 0.4% had clinical information of genital bleeding. Comparing different age-groups, women with genital bleeding had a higher chance of cytological result of high-grade squamous intraepithelial lesion (30-49 years OR 2.38; 1.60-3.53 and ≥ 50 years OR 6.30; 3.72-10.67), squamous cell carcinoma (30-49 years OR 24.70; 11.96–51.03 and ≥ 50 years OR 48.91; 31.28-76.47) and atypical glandular cells (30-49 years OR 5.72; 3.30–9.93 and ≥ 50 years OR 11.56; 5.96-22.45); and a higher chance of adenocarcinoma for women ≥ 50 years (OR 53.13; 28.08-100.51). Women ≥ 30 years old with genital bleeding should be examined by specialized professional to rule out the possibility of cervical cancer.

Key words: Uterine Cervical Neoplasms, Papanicolaou Test, Early Detection of Cancer, Age, Abnormal uterine bleeding.

Abbreviations:

ASC: atypical squamous cells

LSIL: low-grade squamous intraepithelial lesion

HSIL: high-grade squamous intraepithelial lesion

AGC: atypical glandular cells

SCC: squamous cell carcinoma

Introduction

The detection and early treatment of precursor lesions in the cervix has proven to be effective in decreasing the incidence of and mortality from cervical cancer, especially in countries with organized screening programs that achieve high coverage (1). In Brazil, the national guideline recommends to screen women from 25 to 69 years old with cervical smears every three years, after two consecutive annual negative smears (2). Although there is a national policy, screening is opportunistic since there is no invitation strategy to reach the target women.

Some women seek medical evaluation only when symptomatic. Genital bleeding is a common complaint in gynecological visits and even among attendees in general practices, post-coital complaints can have been noted in 6% of menstruating women (3). Since genital bleeding may be the first manifestation of a neoplasia, it has been recommended that the evaluation of genital bleeding should be individualized for each specific age group (4,5). Women with genital bleeding have a higher risk of presenting with abnormal cervical smears (6) and invasive carcinoma (4,7). Moreover higher rates of unsatisfactory smears are seen among women with genital bleeding, since when blood obscures more than 75% of squamous cells, the smear is classified as unsatisfactory quality if there are not altered cells (8).

This study sought to evaluate the possible association of clinical information on concurrent genital bleeding with the quality and results of cervical smears by using a database of 2.5 million smears from screening context in a densely populated urban area in Brazil.

Material and methods

This was an observational analytical study of cervical smear results from the cytopathology laboratory database of Dr. José Aristodemo Pinotti Women's Hospital at Unicamp (State University of Campinas - Unicamp). The laboratory receives smears collected from women originating from almost 70 municipalities in the Campinas region of south-east Brazil and has a long-standing experience in training and research. The study comprised the inclusive period from January 2000 to December 2009 (10 years). Since it is an opportunistic program, the cervical smear is usually obtained during women's regular evaluation with health care providers (nurses, general practitioners or gynecologists). No changes in the provision of cervical cytology local services were observed during the study period. Institutional Review Board approval was obtained from Unicamp (No. 375/2010).

The cervical smear results were reported according to the Bethesda System (8). The categories of atypical squamous cells that do not exclude high-grade squamous intraepithelial lesion (HSIL) and atypical glandular cells that do not exclude neoplasia were included in the categories atypical squamous cells (ASC) and atypical glandular cells (AGC) respectively. Smears were considered unsatisfactory when there was poor sample collection, poor fixation, obscuring inflammation, a bloody smear or other not specified features; while smears were considered satisfactory when they have at least 8000 squamous well preserved cell. For analysis, the unsatisfactory results were differentiated into two groups: unsatisfactory bloody smear and unsatisfactory for other reasons.

From the total of 2 505 154 smears, cases were excluded concerning women who underwent cervical smear for purposes other than screening, who

had had a previous cervical smear test within the last year, had a previous history of cervical neoplastic disease or had undergone radiotherapy or chemotherapy before, making the total 2 324 836 smears. For the analysis of cervical smear quality and clinical information on genital bleeding, women were stratified into two groups: women <50 years old and women aged ≥50 years. For the smear result analysis we also excluded unsatisfactory smears, smears from women <18 years or for whom age was not available in the data, cases with cervical smear results of ASC and low-grade squamous intraepithelial lesion (LSIL). Thus the final sample consisted of 2 167 557 smears (Figure 1). Adenocarcinoma "in situ" and cervical smear results showing invasive adenocarcinoma were analyzed together due to the few cases observed. In this analysis women were stratified into three age groups (18-29, 30-49, ≥50 years).

Data were presented as absolute (n) and relative (%) values. Measuring magnitude of association was done by odds ratios (OR) with 95% confidence intervals (95% CI). The significance level was 5% and the software used was SPSS version 22. When absolute values were lower than 5 per box (n<5) the OR calculation was not performed.

Results

Among the total cervical smears 0.4% had clinical information of concurrent genital bleeding and 1.4% was considered unsatisfactory for analysis. For women with clinical information on genital bleeding and aged <50 years, 4.4% had unsatisfactory smears and 1.9% of these were unsatisfactory because of blood. For women ≥50 years there were 6.3% unsatisfactory smears and 2.4% because of blood. The highly significant association between the

concurrent genital bleeding and bloody unsatisfactory smears, both for women <50 years old (OR 19.03; 95% CI 15.88 - 22.82) and for those ≥50 years (OR 22.52; 95% CI 16.19 - 31.31). There was also an association between unsatisfactory smears for other causes among women <50 years (OR 2.54; 95% CI 2.17 - 2.96) and those ≥50 years (OR 1.64; 95% CI 1.27 - 2.11) (Table 1).

When cervical smear results were stratified by age groups there was no association between genital bleeding and HSIL for women aged 18-29 years (OR 1.43; 95% CI 0.81 – 2.52). Women with genital bleeding had a higher chance of HSIL if they were >30 years (30-49 years, OR 2.38; 95% CI 1.60 - 3.53 and ≥50 years OR 6.30; 95% CI 3.72 - 10.67), SCC (30-49 years OR 24.70; 95% CI 11.96 – 51.03 and ≥ 50 years OR 48.91; 95% CI 31.28 - 76.47) and AGC (30-49 years OR 5.72; 95% CI 3.30 – 9.93 and ≥50 years OR 11.56; 95% CI 5.96 - 22.45); and a greater chance of adenocarcinoma for women aged ≥50 years (OR 53.13; 95% CI 28.08 - 100.51) (Table 2).

Discussion

This study demonstrated that the chances of HSIL, SCC, AGC and adenocarcinoma were higher for women with clinical information of concurrent genital bleeding. Furthermore, the study indicates no relation between genital bleeding and abnormal cervical smear results for women under 30 years old. For women over this age genital bleeding was associated with HSIL, SCC and AGC while adenocarcinoma was only seen among women with genital bleeding over 50 years.

These data are in agreement with previous publications which suggested that genital bleeding for menopausal and perimenopausal women should be considered as an indicator of high risk of invasive carcinoma and precursor lesion (7,9). Considering post-coital bleeding, it has been suggested that association with precursor cervical lesion is due to increased fragility of the epithelium because of the neoplastic process (4).

This study also showed that the chance of a smear of unsatisfactory quality was higher for women where there was clinical information about concurrent genital bleeding. It has been proposed that tumor angiogenesis is the cause of many smears being erroneously classified as unsatisfactory or even negative in cervical carcinoma and precursor lesion cases (10). Some possible explanations for different chances of unsatisfactory bloody smear for the age-groups analyzed are the higher rates of carcinoma and the atrophic alterations frequently found in women over 50 years.

The strength of this study was the large amount of high quality smears available for analysis. No selection was applied and the study used information from 10 years work, providing a good portrait of the population. Weaknesses to be considered include that there was no differentiation between the various types of genital bleeding (intermenstrual, postcoital, spontaneous, peri- or postmenopausal) and information on bleeding was obtained through enquiry by the healthcare professionals who performed the smear, which is known to be susceptible to bias. Moreover, since the Brazilian screening program is opportunistic, high levels of abnormal results can be taking account as consequence of women who looking for health assistance only when they are symptomatic.

Women with clinical information of concurrent genital bleeding have a higher chances of cytological abnormalities even after the age of 30 and in addition of adenocarcinoma after the age of 50 years, and they also have higher rates of unsatisfactory smears. The oldest age group is especially at risk.

Disclosure statement

There are no funding sources

Acknowledgements:

The team of Center for Integrated Health of Women, State University of Campinas, São Paulo - Brazil (CAISM-Unicamp/ Brazil).

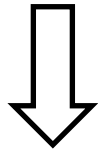
References:

1. Muller CY, Smith HO. Cervical neoplasia complicating pregnancy. *Obstet Gynecol Clin North Am.* 2005;32(4):533-46.
2. Brazilian Cervical Cancer Screening Guidelines. Rio de Janeiro: INCA, 2011.
3. Shapley M, Jordan K, Croft PR . An epidemiological survey of symptoms of menstrual loss in the community. *Br J Gen Pract.* 2004;54:359–63.
4. Rosenthal AN, Panoskaltsis T, Smith T, Soutter WP. The frequency of significant pathology in women attending a general gynaecological service for postcoital bleeding. *BJOG.* 2001;108:103-6.
5. Viikki M, Pukkala E, Hakama M. Bleeding symptoms and subsequent risk of gynecological and other cancers. *Acta Obstet Gynecol Scand.* 1998; 77: 564-9.

6. Wong HY, Loke AY, Chan NH. Risk factors for cervical abnormalities among hong Kong Chinese women: a large-scale community-based cervical screening program. *J Womens Health (Larchmt)*. 2011;20:53-9.
7. Kotaniemi-Talonen L, Malila N, Anttila A, Nieminen P, Hakama M. Intensified screening among high risk women within the organised screening programme for cervical cancer in Finland. *Acta Oncol*. 2011;50:106-11.
8. The revised Bethesda System for reporting cervical/vaginal cytologic diagnoses: report of the 1991 Bethesda workshop. *Acta Cytol*. 1992; 36(3): 273-6.
9. Astrup K, Olivarius N de F. Frequency of spontaneously occurring postmenopausal bleeding in the general population. *Acta Obstet Gynecol Scand* 2004; 83: 203 – 7
10. Boon ME, Ouwerkerk-Noordam E, van Leeuwen AW, van Haften-Day C. Clinical and diagnostic significance of blood in cervical smears. *Diagn Cytopathol*. 2003;28:181-5.

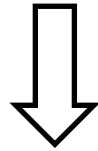
Figure 1: Flow chart on the accumulation of data

Total population 2505154 smears



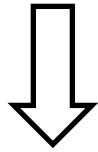
Smears from women who had had a previous cervical smear test within the last year, had a history of cervical cancer, or those that had been submitted to radiotherapy or chemotherapy was excluded (180318 smears were excluded).

2324836 smears



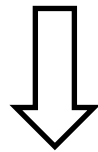
Unsatisfactory quality smear was excluded (33276 smears were excluded).

2291560 smears



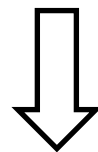
Cases with missing age or missing cervical smear result was excluded (916 smears were excluded).

2290644 smears



Smears from women aged below 18 years were excluded (88572 smears were excluded).

2202072 smears



Smears with diagnosis of ASCUS, LSIL and other neoplasias different from HSIL, SCC, AGC and adenocarcinoma was excluded (34515 smears were excluded).

2167557 smears

Final population

Tables

Table 1: Association between clinical information of genital bleeding and quality of smear stratified in two age-groups

Age	Clinical information of bleeding	Quality			Total
		Satisfactory	Unsatisfactory for other causes	Unsatisfactory bloody smear	
Under 50 years	With bleeding	6359 (95.6%)	169 (2.5%)	127 (1.9%)	6655 (0.4%)
	Without bleeding	1 838 462 (98.9%)	19 262 (1.0%)	1929 (0.1%)	1 859 653 (99.6%)
	OR ¹ (CI ² 95%)	1	2.54 (2.17 – 2.96)	19.03 (15.88 – 22.82)	---
50 years or more	With bleeding	1530 (93.8%)	63 (3.9%)	39 (2.4%)	1632 (0.4%)
	Without bleeding	445 209 (97.4%)	11183 (2.4%)	504 (0.1%)	456 896 (99.6%)
	OR ¹ (CI ² 95%)	1	1,64 (1.27 – 2.11)	22,52 (16.19 – 31.31)	---

1: OR: odds ratio

2: CI Confidence interval.

Tabela 2: Cervical smear results in women with and without genital bleeding stratified by age-group

		Cervical smear result				
		Negative ¹	HSIL ²	SCC ³	AGC ⁴	Adenocarcinoma ⁵
18 – 29 years old	With bleeding	2 133 (99.3%)	12 (0.6%)	0 (0.0%)	2 (0.0%)	0 (0.0%)
	Without bleeding	707 661 (99.6%)	2 780 (0.4%)	8 (0.0%)	144 (0.0%)	3 (0.0%)
	OR ⁶ (CI ⁷ 95%)	1	1.43 (0.81 – 2.52)	*	*	*
30 – 49 years old	With bleeding	3 828(98.7%)	25 (0.6%)	8 (0.2%)	13 (0.3%)	3 (0.1%)
	Without bleeding	1 004 760 (99.6%)	2 760 (0.3%)	85 (0.0%)	596 (0.1%)	44 (0.0%)
	OR ⁶ (CI ⁷ 95%)	1	2.38 (1.60 – 3.53)	24.70 (11.96 – 51.03)	5.72 (3.30- 9.93)	*
50 - 98 years old	With bleeding	1413 (96.2%)	14 (1.0%)	22 (1.5%)	9 (0.6%)	11 (0.7%)
	Without bleeding	440 094 (99.7%)	686 (0.2%)	138 (0.0%)	241 (0.1%)	64 (0.0%)
	OR ⁶ (CI ⁷ 95%)	1	6.30 (3.72 – 10.67)	48.91 (31.28 – 76.47)	11.56 (5.96 – 22.45)	53.13 (28.08 – 100.51)

*Uncalculated (n< 5 in casela)

1: Negative: negative for intraepithelial lesion or malignancy

2: HSIL: high-grade squamous intraepithelial lesion

3: SCC: invasive squamous carcinomas

4: AGC: atypical glandular cells

5: Adenocarcinoma: adenocarcinoma “in situ” and invasive adenocarcinoma

6: OR: odds ratio

7: CI: Confidence interval.

Capítulo III: Conclusões

1. Controlada a idade, idade de início da atividade sexual e intervalo entre exames não há diferença quanto a prevalência de HSIL mulheres gestante e não-gestantes, podendo as mulheres gestantes serem acompanhadas segundo os protocolos vigentes para as mulheres não-gestantes. Dessa forma, sugere-se que o exame de citologia cérvico-vaginal possa ser abandonado como rotina obrigatória do pré-natal.
2. Existe associação entre HSIL e idade de início da atividade sexual: quanto mais precoce a idade de início da atividade sexual, maior a chance de HSIL.
3. Intervalo entre exames de citologia cérvico-vaginal maior ou igual a cinco anos está associado a HSIL para mulheres a partir de 21 anos.
4. Informação clínica de sangramento genital está associada a maiores taxas de HSIL, carcinoma de células escamosas e atipia de células glandulares para mulheres a partir de 30 anos, e adenocarcinoma a partir de 50 anos.
5. Mulheres com informação clínica de sangramento genital possuem maiores taxas de esfregaço com qualidade insatisfatória para análise.