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CERVICAL HEMANGIOMA IN PREGNANCY

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Abstract

Hemangioma in the uterine cevix is a rare case, especially during pregnancy. Hemangioma is a benign tumor, but it can cause complication namely antepartum bleeding, preterm labour, and severe, life threatening complication such as disseminated intravascular coagulation (DIC). Histopathology examination is needed to diagnose hemangioma, and to differentiate this disease with other pathological condition. Conservative therapy was chosen as the main option rather than surgical therapy. The case report explain about 2 cases with cervical hemangioma in the uterine in 2 pregnant women. In the case 1 we presented a 27 years old primigravida, 29th weeks gestational age, with antepartum bleeding. A cervical biopsy was done and the histopathological examination reveal a capillary hemangioma within the uterine cervix. The patient was followed up with medications, and a caesarean section was planned to deliver the baby. In the case 2, a 30 years old multigravida with complained of postpartum bleeding. The clinical manifestation of cervical hemanioma in pregnancy was similar with other pathological condition, such as cervical cancer. A better understanding in pathogenesis and histopathological examination is important to differentiate hemangioma and other pathological condition in uterine cervix. Therapeutic modality was still debated, because of the limitation of literature about hemangioma cervix, especially in pregnant women.

Keywords: hemangioma; uterine cervix; pregnancy

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Introduction

Hemangioma is one of the most common soft tissue and cutaneus tumor, with prevalence in pediatric patients around 4%-5%, dominated in female population (2.5 higher than male). The incidence was increased in Caucasians (Wildgruber, Sadick, Müller-Wille, & Wohlgemuth, 2019). Several classification of hemangioma were devided according to vascular type (capillary, cavernous, venous), locations (cutaneus, intramuscular), the predominance of cells (epithelial cells, spindle), ages (juvenile, senile), and the nature of the disease (neoplasm, malformations, teleangiectasia) (Djolai et al., 2015). Hemangiomas located on the female genital tract are extremely rare, with only less than 100 cases reported through case reports in recent years (Djolai et al., 2015) (Shah & Raju, 2018).

Pathogenesis of hemangioma in the cervix and other female genital tract is still unclear, however the hormonal stimulation may play a role in the pathogenesis. The clinical manifestation of hemangioma in the uterine cervix present in broad spectrum, ranging from asymptomatic to several complains including abnormal vaginal bleeding, abdominal pain, antepartum bleeding, post-coital bleeding, and foreign body sensation in the vaginal introitus (Ogunlaja, Ano-Edward, Ogunlaja, & Lasisi, 2020) (Busca & Parra-Herran, 2016) (Mahapatra et al., 2013). Obstetrical

complication including premature rupture of membrane, fetal death in-utero, post-partum bleeding, and disseminated intravascular coagulation (DIC) (Virk, Zhong, & Lu, 2009) (Elkhateb et al., 2011). Indirect effect that could be happen in fetus and neonatus include perinatal mortality, respiratory distress syndrome in newborn, intraventricular haemorrhage, and hypoplastic lung (Hong PL, 2021).

Antepartum bleeding complaints in hemangioma could be similar to other pathology, such as cervical cancer or placenta previa. It is importnat to differentiate hemangioma form other pathology through history taking, physical examination, and histopathological examination to confirmed the diagnosis (Busca & Parra-Herran, 2016). With the right diagnosis, the clinicial could decide the right therapy for the patients.

Therapeutical modalities are still controversial. Conservative therapies options were excision with carbondioxide laser, cryotherapy, and surgical excision. Refractory hemangioma may require hysterectomy as a last option (Ogunlaja et al., 2020). Because the rarity of this case, and similar clinical manifestation with other pathological condition in the uterine cervix (e.c cervical cancer), it is important to know how to diagnose hemangioma in the uterine cervix. With a good diagnostic approach, the clinician could choose the exact therapy according to individual characteristics.

This case report explained about 2 cases of hemangioma in uterine cervix. The first case presented 27 years old with 29th weeks gestational age with antepartum bleeding. Biopsy was done and the patient was followed up with several medications. Sectio caesarean was planned to prevent complications. The second case presented 30 years old multigravida with chief complain bleeding and leaking of watery fluid from vagina. The baby was born pervaginal, but there was post partum bleeding caused by hemangioma in the cervix. This case report presented to increase awareness of the possibility of hemangioma in the uterine cervix throughout pregnancy that can present as antepartum bleeding, where as this can be a life-threatening event if not treated appropriately.

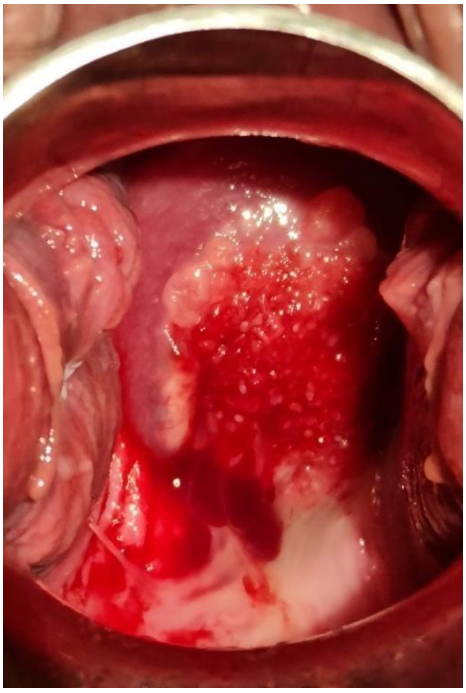
Method

In the first case we presented a 27 years old woman, primigravida, with 29th weeks gestational age. She complained about vaginal bleeding since this last 6 days. Other complain such as abdominal pain, gushing or leaking watery fluid from vagina was denied. The patient had her first sexual intercourse at the age 16th, and there was history of multiple sexual partners (two different people). She had not been vaccinated with HPV vaccine. History of smoking and alcohol drinking was denied. There was no history of malignancy in either the patient nor the family. She had her first period at the age of 14th years, with regular cycle within 30 days, duration of menstruation in 4 days, and volume estimation 50 cc. Previous history of contraceptive use was denied. From the history taking the clinicial suspect there was a placental problem.

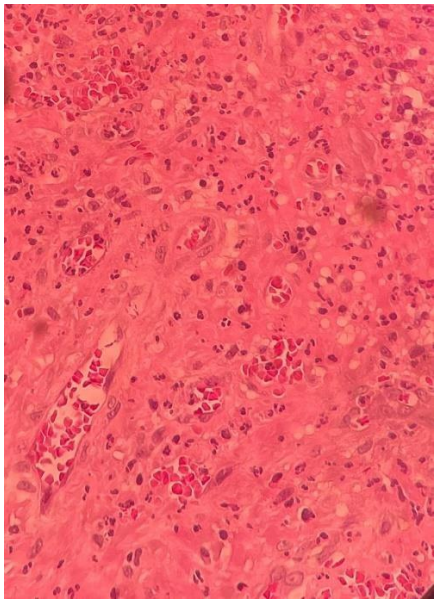
Vital sign and general status within normal limits. On Leopold examination, the fetal had longitudinal lie and cephalic presentation. Inspeculo examination showed an irregular mass with brittly surface, easly bleeds, on the anterior and left lateral portion of cervix, with size estimation about 3x3 cm, actively bleeding. On ultrasonography examination showed a single life fetus, 29th weeks gestational ages, with positive fetal heart beat. The placenta located in the fundus anterior, there is no found placenta previa, and amniotic fluid measures by single deepest pocket (SDP) is 4,18. Laboratory examination result showed in Table 1.

Table 1
Laboratory result

Indicator	Result	
Haemoglobin	12,4 g/dL	Normal
Haematocrite	38%	Normal
Leucocyte	15,72 x 10^3/uL	High
Thrombocyte	450 x 10^3/uL	Normal
MCV	80,4 fL	Normal
MCH	26,2 pg	Low
MCHC	32,6 g/dL	Normal
Basophil	0,4%	Normal
Eosinophil	0,9%	Normal
Neutrophil	72,5%	Normal
Monocyte	4,3%	Normal
Limfocyte	21,9%	Normal



Picture 1
Macroscopic view on hemangioma in the uterine cervix



Picture 2
Microscopic view of cervical mass (Case 1). There were vascular proliferation, with round shape, lined by endothelial cells. There were no sign of atypia, and the lumen contained erythrocytes.

A biopsy performed for histopathological examination. The patients received several therapy, including 500cc of Ringer Lactate, tranexamic acid 1 gram every 8 hours intravenously, paracetamol 500 mg every 8 hours peroral, amoxicillin 500 mg every 8 hours peroral, and vaginal tampon for 1x24 hours. Pregnancy was followed up, and caesarean section was planned for delivery to avoid vaginal bleeding due to manipulation of hemangioma.

Histopathological examination showed a tumors arranged in lobulated structure, on one part lined by mucinous columnar epithelial cells, and the other part lined by squamous epithelial cells, without any signs of dysplasia. There was also vascular proliferation, with round shape, layered by endothelial cells. There were no sign of atypia, and the lumen contained erythrocytes. Infiltration of neutrophil with stromal foci was shown, indicating decidual reaction. With these results, we conclude the lesion as lobular capillary hemangioma.

In the second case, we present a 30 years old multigravida with chief complain spotting and bleeding during 1st trimester until 3rd trimester of pregnancy. First complain occured during 12th weeks of pregnancy. She came to the health facility with spotting at last 3 day. The patient received a conservative therapy. The same complaint repeated at 28th weeks of gestation. On inspeculo examination, a spongy mass that easly bleed found on the cervix, and cervical cancer was suspected. At 31st weeks of gestational age, the patient compalined bleeding and mucoid discharge form the birth canal. The pregnancy could be maintained. The same experienced happen at 34th weeks of pregnancy, and followed by regular contraction. The fetal movement was in normal range. The patient had her first sexual intercourse at the age of 17 years old, and history of sexual intercourse with more than one partner was denied. History of HPV vaccine, smoking, and alcohol drinking was denied. There is no family history of malignancy. The patient had her first menstruation at the age of 15th years old, with regular cycles every 30 days, duration of 4 days, and volume approximately 50 cc. The patient used an intrauterine device (IUD) as contraception of choice, and was removed 1 years ago (before planning on pregnancy).

Vital sign and general examination within normal limits. On Leopold examination, the fetus had longitudinal lie, with cephalic presentation and had entered the pelvic inlet. On bimanual examination, there was already 4cm opening and 60% effacement. The patient has entered first stage of labor, and a baby boy was born with 1630 gram birth weight. The baby had a seizure than pronounced dead shortly after birth.

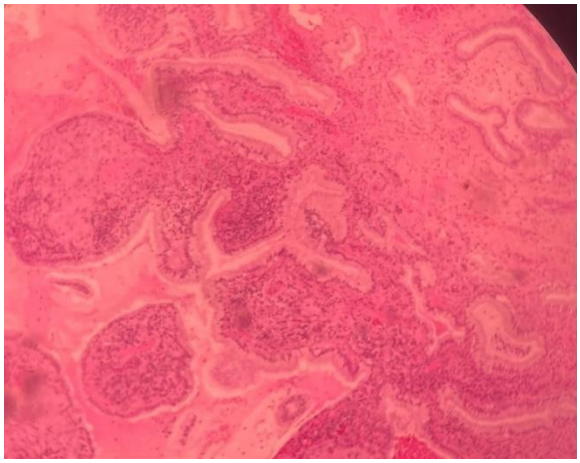
Two months later, the patient came with bleeding from genital tract, not accompanied by vaginal discharge nor abdominal pain. On inspeculo examination shown a mass with irregular surface, size about 3x3 cm, and accompanied by active

bleeding. Laboratory examination and biopsy were performed, as seen in table 2.

The clinician suggested to do hemangioma excision, but refused. The patient want another option of therapy.

Tabel 2
Laboratory examination in the second case

Indicator	Result	
Haemoglobin	10,9 g/dL	Low
Haematocrit	32,4	Low
Leukocyte	18,2 x 10^3/uL	High
Thrombocyte	256 x 10^3/uL	Normal
MCV	96 fL	Normal
MCH	32,3 pg	Menurun
MCHC	33,6 g/dL	Normal
MID%	11.5%	Normal
GRA%	73.3%	Normal
LYM%	15,2%	Normal
Bleeding Time	1 menit	Normal
Clotting Time	8 menit	Normal



Gambar 3
Microscopic view of tissue biopsy (Case 2)

Histopathological examination showed a tumor tissue in the ectocervix, formed a lobulous structure, consisting of blood vessel, some of them are dilated and thin-walled. The blood vessels were lined by a thin endothelial layer, without any signs of atypia. The lumen contained erythrocytes. In the other part of tissue, endocervical tissue was seen, lined with layer of mucinous columnar epithelium, without any signs of dysplasia. The stroma contaned densed infiltration of lymphoplasmic chronic inflammatory cells. From these result, we conclude this lesions as capillary lobular hemangioma, with chronic endocervicitis.

Results and Discussion

According to the International Society for the Study of Vascular Anomalies (ISSVA) classification, hemangioma is a benign vascular tumor caused by abnormal proliferation of blood vessel, and it can occur mostly in the cutaneus layer, or internal organ. Hemangioma originated from capillaries, veins, lymphatic tissue, arteriovenous, or the combination of these tissues (Mahapatra et al., 2013) (Karpathiou, Chauleur, Da Cruz, Forest, & Peoc'h, 2017). Hemangioma are rarely found in the female genital tract, especially in the uterine cervix. There are few cases reports that discuss hemangioma in the uterine cervix (Karpathiou et al., 2017) (Shopov, 2020) (Busca & Parra-Herran, 2016) (Shah & Raju, 2018). Cervical hemangioma occured during preganancy have been reported in several case reports. There were 2 cases reported from India in 3rd trimester pregnant women (respectively 34th weeks and 37th weeks gestational age) (Pal R, 2013) (Mahapatra et al., 2013). One case in Morocco found in pregnanct woman with premature rupture of membrane at 32nd week gestational age (Elkhateb et al., 2011), and 1 case in Japan with 6th weeks gestational age (Tanaka et al., 2007).

Pathogenesis of hemangioma is still debated, however if judged from the age distribution and several documented expression of hormone receptor, sex hormones may be involved in inducing vascular and endothelial cell proliferation. Although hemangioma can occur in children to elderly population, hemangioma in the uterine cervix predominates in reproductive age and during pregnancy (Shopov, 2020) (Pal R, 2013) (Busca & Parra-Herran, 2016) (Mahapatra et al., 2013). Estrogen are

known for their proliferative effect in endothelial cells in vitro, and this hormone could also interact with Vascular endothelial growth factor (VEGF). VEGF is a potent angiogenic factor that could stimulate proliferation, migration, and vascular formation. Estrogen also induced production of other angiogenic factors such as basic fibroblast growth factor (bFGF), insulin-like growth factor (IGF), and tranforming growht factor beta (TGF beta). Other roles of estrogens in the pathogenesis of hemangioma were expressing vascular adhesion molecules and integrins, as well as inhibiting endothlelial cell apoptosis (Sun et al., 2008). Estrogen and progesterone receptors were also expressed on endothelial cells and stromal cells. From this information, we suspected that progesteron also took a role in pathogenesis of hemangioma (Busca & Parra-Herran, 2016). Vascular lesion in the uterine cervix may also caused by uterine damage, or leiomyoma that could interfere the normal vascularisation in the cervix (Karpathiou et al., 2017).

Hemangioma of the female genital tract might involve the uterine body and/or cervix, with the uterine body more commonly involved. In our cases, hemangioma were both located in the uterine cervix, without involvement of other parts of the uterine. Based in the morphology, hemangioma were classified into several types, namely capillary, cavernous, and venous hemangioma. Capillary hemangioma sonsist of several intersecting capillaries. In comparison, cavernous hemangioma were well demarcated, larger in size, located deeper in the submucosal layer, and did not cause changes the uterine cervix (Djolai et al., 2015). Several literatures showed that cavernous hemangioma were more common than capillary type histopahologically (Shopov, 2020) (Pal R, 2013) (Mahapatra et al., 2013) (Elkhateb et al., 2011). In contrary, the histopathological examination in our study found that both hemangioma were capillary hemangioma.

Clinical manifestations of hemangioma in the uterine cervix presented in broad spectrum. The complaints ranging from asymptomatic to several complaints such as abnormal vaginal bleeding, abdominal pain, antepartum bleeding, postcoital bleeding, and foreign body sensation in the vaginal introitus (Ogunlaja et al., 2020) (Busca & Parra-Herran, 2016) (Mahapatra et al., 2013). Due to their relatively small size, cervical hemangioma were found accidentally on inspeculo examination. In a study conducted by Busca et al on 48 subjects, 31.3% had no symptoms, 56,3% had abnormal uterine bleeding, 6.3% complained post-coital bleeding, 4.2% had postpartum haemorrhage, and 2.1% presented by pelvic pain. Symptoms that commonly found in patients with hemangioma in the uterine cervix during pregnancy include preterm premature rupture of membrane (Elkhateb et al., 2011), foreign body sensation in the vaginal introitus (Mahapatra et al., 2013), antepartum bleeding (Pal R, 2013), or a combination of these symptoms. From previous studies, hemangioma mostly found in the third trimester of pregnancy. In this case report, the woman in the first case was diagnnosed with hemangioma in the cervix in the 3rd trimester of pregnancy, with chief complaints of antepartum bleeding. On the other hand, patient in the second case was diagnosed with cervical hemangioma in the postpartum period, with chief complaints of postpartum bleeding.

Study conducted by Riggs et al stated there were several complications occur in the pregnancy caused by hemangioma, namely premature rupture of membranes, preterm labor, fetal death in utero, post partum haemorrhage, and DIC (Pal R, 2013) (Elkhateb et al., 2011). In the first case, conservative therapy was choosed because there were no sign of preterm labour (partus prematurus imminens), and the pregnancy is still in 34th weeks. Caesarean section was planned as delivery modality to avoid further bleeding. Meanwhile in the second case, the

baby was delivered pervaginal because the presence of preterm labor. The cervical hemangioma was later found in the post-partum period, with the patients complained about postpartum bleeding.

Majority of hemangioma was benign, so the conservative therapy was choosed in majority of cases, but surgical therapy such as hysterectomy, may be conseidered in some cases (Ozyer et al., 2006). Several conservative therapy, such as cryotherapy, radiotherapy, use of sclerotic agents, carbon dioxide laser, electrocautery, and surgical excision, could be done for women who still preserved their fertility (Shopov, 2020). Combination therapies also could be used, such as local excision and electrocautery. Electrocautery functioned to stop the bleeding, while preserving the tissue architecture for histopathological examination (Ogunlaja et al., 2020).

Transarterial catheter embolization was the treatment of choice in rapidly growing hemangioma (Shah & Raju, 2018). These procedures carry risks to fertility and pregnancy, so hemangioma in nulliparous and asymptomatic could be managed expectantly (Ozyer et al., 2006). Hysterectomy were rarely performed as the primary treatment for hemangioma. This surgical therapy only performed if the patient did not respond to conservative therapy or excision, or the patients fell into uterine atonia and/or DIC (Mahapatra et al., 2013) (Elkhateb et al., 2011) (Benjamin, Yaakub, Telesinghe, & Kafeel, 2010). Caesarean section were preferred mode of delivery according to majority of literatures. This modality aims to avoid acute bleeding due to rupture of hemangioma and obstructed birth canal due to the mass pressure effect. If there were obstetrical complication such as premature rupture of membrane, preterm labor, fetal death, post partum haemorrhage, and DIC, caesarean section was chosen as the main mode of delivery (Pal R, 2013) (Mahapatra et al., 2013) (Elkhateb et al., 2011). In the case 2, the baby was born pervaginal.

Hemangioma was discovered later in inspeculo examination after the patient complained bleeding from the birth canal 2 months after delivery. Based on the research by El Khateb et al, vaginal delivery was not impossible for cervical hemangioma, but delivery by caesarean section was preferred by considering the benefits and risks to the patients (Elkhateb et al., 2011). Vaginal delivery could be performed if there were no sign of rapid increased in size of the hemangioma, anatomic distortion, vaginal obstruction, bleeding, and failu to undergo physiological changes (Ozyer et al., 2006).

Patients with cervical hemangioma during pregnancy had similar complaints to other diseases, such as postcoital bleeding, antepartum bleeding, and foreign body sensation in the vaginal introitus. It is important to be able to distinguish hemangioma from other pathological condition that caused similar complaints and could be life threatening, such as cervical cancer and placenta previa.

Placenta previa occured when the ostium internum of uterine was partially or fully covered by the placenta. It is a major risk for post partum bleeding. The main complain include painless bleeding in 2nd or 3rd trimester of prgenancy, induced by sexual intercourse, uterine contraction, or repeated vaginal examination (Anderson-Bagga & Sze, 2019).

Some cases could be detect sooner with routine ultrasonography examintaion thorough out the first trimester. Low-lying placenta (when placenta located 2 cm until 3.5 cm from ostium internum) resolved in the 3rd trimester because of placental migration. If there were evidence of low-lying placenta, followed-up USG were recommended at 28th until 32nd week of pregnancy, to observed the persistent of low-lying placenta. Patient with painless bleeding at 2nd or 3rd trimester of pregnancy should be examined with transabdominal USG before digital examination. If placenta previa was suspected, transvaginal USG was

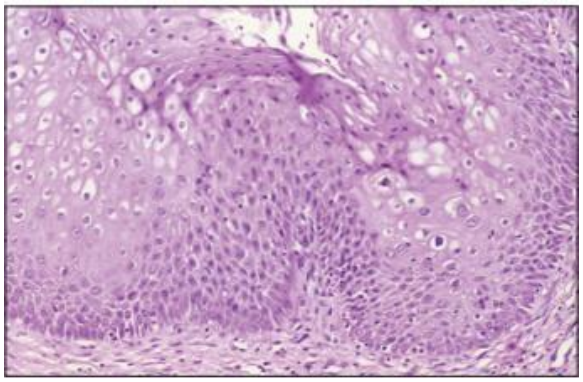
recommended and safe to examine the patient (Anderson-Bagga & Sze, 2019).

With diagnosis of placenta previa, mode of delivery that recommended was elective caesarean section at 36th until 37th weeks of pregnancy. If patient with known history of placenta previa and ongoing painless bleeding, the clinician should assessed their vitals, and evaluate fetal well-being. The patient should receive 2 intravenous line with large caliber, and performed crossmatching for transfusion preparation. If excessive bleeding occured, or there were fetal complication, emergency caesarean section was performed. If the bleeding stop, expectant management was recommended if the gestational age is less than 36th weeks. If the gestational age was at or greater than 36th weeks, termination of pregnancy was recommended. The urgency for inpatient treatment decided based on patient and fetal stability, patient compliance, and proximity to the neares hospital (Anderson-Bagga & Sze, 2019).

Clinical manifestations of cervical cancer in pregnancy had a farily broad spectrum, depending on the clinical stage and the size of the mass. Common symptoms that usually found include purulent vaginal discharge with specific odor, often accompanied by blood, and irregular bleeding. Cervical cancer in advance stages presented with abdominal pain, and chronic anemia may occur due to prolonged irregular bleeding (Anderson-Bagga & Sze, 2019) (McDonald, Faught, & Gruslin, 2002). These symptoms were rarely found in cervical hemangioma, which presented as antepartum bleeding, or mass/foreign body from the introitus. Risk factor of cervical cancer need to be explored further during anamnesis, for example history of Human Papilloma Virus (HPV) infection and vaccination, early age at first sexual intercourse, number of sexual partners, number of pregnancy and parturition, and smoking status .

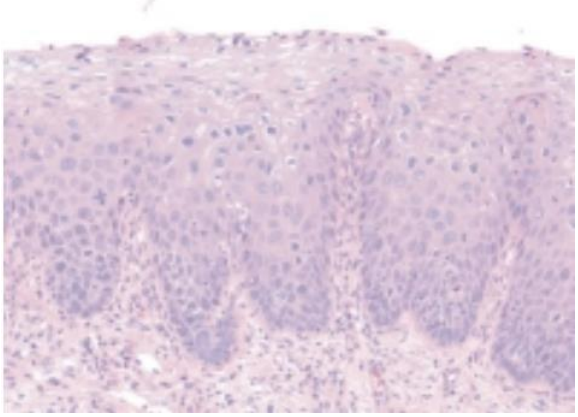
Every pregnant woman with antepartum bleeding should have a gynecological examination and cytological screening. Cervical cancer screening in pregnancy was carried out through 3 stages, cytological examination, colposcopy, and cervical biopsy (Li, X., Wang, Y., & Yu, 2015) (McDonald et al., 2002) (Beharee, Shi, Wu, & Wang, 2019). Cytological examination was the first choice for rapid diagnosis of cervical cancer. This examination was carried out using cytobrush, and safe for the mother and the fetus. Interpretation should be carried out by an experienced pathologist, because misdiagnosis could occur due to several physiological changes in the cervix during pregnancy. These changes was caused by increased level of estrogen and progesterone. Both hormones caused glandular hyperplasia of the cervical mucosa, migration of the squamo-columnar junction, proliferation of basal cells, irregular cells morphology, and enlargement of the nucleus (Beharee et al., 2019). Colposcopy without biopsy was less accurate to estimate the severity of cervical lesions during pregnancy, due to physiological changes in the cervix. Colposcopy was best used during the first and second trimester of pregnancy. Cervical biopsy was done on high grade lesions or suspected cancer, with or without colposcopy. Biopsy did not increase risk of complication during pregnancy, spontaneous abortion, and preterm birth, but it should be noted that the cervix was easily bleeds during pregnancy. If the biopsy area was too large or too deep, the risk of heavy bleeding and spontaneous abortion was increased. To minimize these risks, the biopsy was performed on all visible lesion with maximum depth of 1 cm (Beharee et al., 2019) (Tarney & Han, 2014). Histopathological findings in cervical cancer was described based on the classification of cervical intraepithelial neoplasia (CIN), which included all precancerous lesions that had a potential to become an invasive cancer. This classification divided the lesions into 3 categories, namely CIN 1, CIN 2, and CIN 3. CIN 1 lesions described as epithelial hyperplasia, seen from the increased in the

thickness of basal and parabasal layers, and the presence of koilocytosis, hyperkeratosis, or dyskeratosis (Jenkins, 2007).



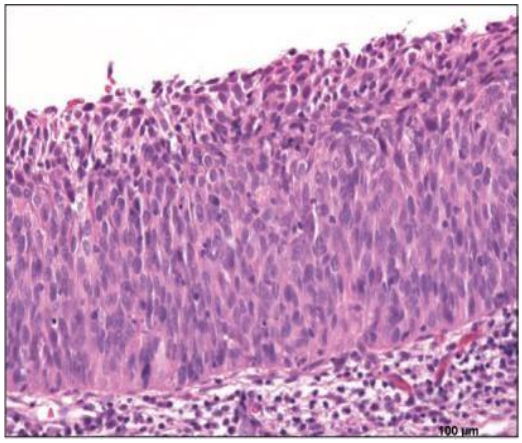
Picture 2
CIN 1 on uterine cervix biopsy (magnification 20x)[27]

CIN 2 were a transitional lesion and used as a borderline for starting cervical cancer therapy. Criteria for CIN 2 include nuclear atypia more severe than CIN 1, aneuploidy, presence of proliferative immature cells up to 2/3 of the epithelium, abnormal mitoses in the epithelium, and koilocytosis, accompanied by apoptotic or dyskeratotic cells (Jenkins, 2007).



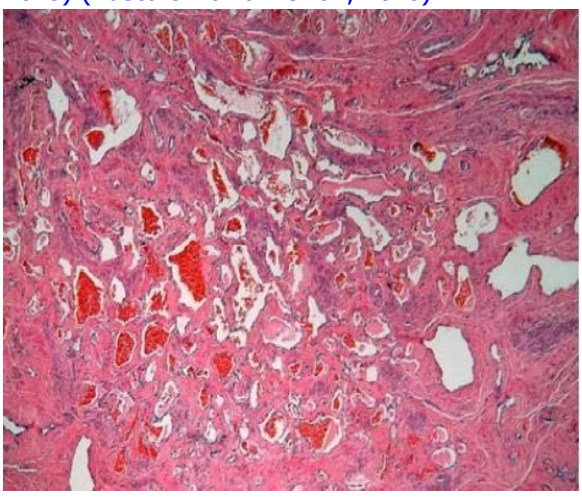
Picture 3
CIN 2 on cervical biopsy (magnification 20x)(Jenkins, 2007)

The hallmark of CIN 3 were the loss of mature epithelial architecture, with more than 2/3 epithelium consist of abnormal and immature cells, and the presence of atypical mitoses and abnormal nuclei (S., 2011).



Picture 4
CIN 3 on cervical biopsy (magnification 20x)[27]

Typical appearance on histopathological examination of hemangioma include benign proliferation of blood vessels, which are lined with endothelium. Proliferation could be located in only one layer, or transmural. In capillary hemangioma, the blood vessel was smaller in size and cross each other, meanwhile in cavernous type, the blood vessel was larger and made a cavernous pattern (Djolai et al., 2015) (Busca & Parra-Herran, 2016).



Picture 5
Cavernous hemangioma in uterine cervix, with hematoxylin eosin and magnification 40x[2]

Conclusion

Hemangioma located in uterine cervix is a very rare condition. This disease had

severe; gynecological and obstetric complications. The diagnosis was confirmed by histopathological examination to distinguish it from other diseases such as cervical cancer. Classical appearance of hemangioma is benign proliferation of blood vessels. The recommended mode of delivery is caesarean section. Hemangioma can be treated first with conservative therapies, but hysterectomy may be an option if life-threatening complications are present.

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