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The Success of Pulp Revascularization in Pregnant Women: A Literature Review

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Abstract

This article presents a literature review, which aims to establish a link between the success of pulp revascularization as a new therapeutic approach of teeth with necrotic pulp, and the state of pregnancy in women. The success of pulpal revascularization depends essentially on the availability of stem cells and the presence of growth factors that will direct the differentiation of these cells to a specific cell line. An electronic search was conducted on PUBMED, Cochrane, and Journal of Endodontics using the following keywords: pulp revascularization, pregnancy, growth factors, dental pulp stem cells. Then, and in order to identify items that would have escaped the electronic search, a manual search was performed from the list of pre-selected items.

Keywords: Pulp revascularization; Pregnancy; Growth factor; Stem cells

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Introduction

The dental pulp is subject to severe damage due to tooth caries or trauma. The recommended conventional therapy is endodontic treatment, which consists of the removal of the entire dental pulp and the filling of the pulp space with inert materials. This treatment induces a weakening of the tooth and a greater susceptibility to infections. But with the progress of regenerative medicine, bioengineering techniques now make it possible to rebuild organs from stem cells.

Revascularization is a new therapeutic approach for immature teeth with necrotic pulp. It is also a good alternative to organic bases which, unlike artificial apical barrier techniques, allows further root development and recovery of pulp vitality. It is based on tissue regeneration based on multidisciplinary principles to maintain tooth functionality, including growth factors, biomaterials and stem cells. It is now accepted that the manipulation of these three factors can ensure the regeneration of functional pulp tissue [1]. This situation is often encountered during pregnancy in women where we observe an increase in the contribution of these 3 elements.

Oral care for pregnant women often remains a source of questions and doubts for patients, but also for health professionals, who, for fear of damaging the proper course of pregnancy, postpone dental care to a later period after delivery or even after breastfeeding. However, the current recommendations go against this abstention from care [2].

The management of a pregnant patient must be rational. The aim is to eliminate the symptomatology and allow her to continue her pregnancy in good conditions.

The aim of this article is to highlight the process of pulpal revascularization as a new therapeutic approach, and to understand the mechanism by which pulp stem cells give birth to a new pulp, and thus study the relationship between pregnancy in women and the success of revascularization therapies.

Concept of Pulp Revascularization

During its formation, the permanent tooth can be subjected to several aggressions, such as caries or trauma. These aggressions damage the pulp tissue, and can cause its necrosis in certain situations. This necrotic state can cause infectious problems. The management of this type of case has long been limited to cleaning/disinfection/obturation of the endodontic system [1].

Endodontics is at a decisive turning point, its once mechanical approach is now becoming more and more biological and regenerative. Indeed, research in pulpal biology has made it possible to develop new pulpal regeneration therapies with the aim of preserving a living dental organ on the arch [3].

These concepts are not recent, as early as 1961, Nygaard Ostby showed that it was possible to induce the formation of vascularized tissue in the canal of a necrotic tooth with an apical lesion, they placed a blood clot after overinstrumentation, cleaning and disinfection of the canal, assuming that the blood clot would have the ability to support the growth of a new tissue [3]. But it was only in 2001 that new procedures such as pulp revascularization itself was developed using platelet concentrates or based on human model gene therapy, which demonstrated the continued formation of root structures and clinical evidence of sensory responses.

Pulp revascularization is a regenerative treatment of necrotic immature teeth that consists of inducing the formation of a blood clot within the previously disinfected canal, involving the recruitment of stem cells from the apical region. The objective of this therapy is to regenerate tissue comparable to pulp tissue and to reactivate dentinogenesis, which has become non-existent due to necrosis of the pulp tissue, and subsequently allows the root to develop [4].

Several types of stem cells including dental pulp stem cells (DPSC), stem cells from human exfoliated deciduous teeth (SHED), and stem cells from the apical papilla (SCAP) have the ability to produce osteoid and odontoid structures. SCAP are cells located at the level of the loose connective tissue at the tip of the apex, they are similar to those of the pulp, and these SCAP are the source of the main odontoblasts that are responsible for completing the development of the root [5].

Stem cell proliferation and differentiation processes are enabled through gene transcription activity, which is regulated by transcription factors. These modify gene expression and provide information on cellular functions. Gene transcription is achieved through the activity of RNA polymerase. To initiate transcription, proteins specific to each cell type are expressed.

The pre-requisite for differentiation is the existence of an undifferentiated state, maintained by the existence of growth factors, cytokines, intercellular contacts, extracellular matrix.

The differentiation of pulp stem cells into a specific cell line is determined mainly by the components found in their microenvironment, such as growth factors, receptors, signalling molecules, transcription factors and extracellular matrix proteins.

Immunohistochemical markings and in situ hybridizations have shown the presence of growth factors and their receptors during the differentiation of pulp stem cells. The effect of these molecules on cell differentiation was tested *in vitro.*

Table 1 below summarizes the different growth factors identified by immunohistochemical markers in the pulp environment and their action on revascularization.

These growth factors initiate the migration of stem cells within the root canal and are an essential element in the revascularization process.

Indeed, after the elimination of microorganisms and necrotic tissues from the canals of necrotic immature teeth, these stem cells can populate the canal space and form a new pulp tissue [5].

Several clinical studies [6-19] have shown the possibility of inducing pulp revascularization on immature teeth after the introduction of tri-antibiotic therapy based on metronidazole, ciprofloxacin and minocycline [20,21]. This triantibiotherapy is placed at the level of the disinfected ductal system, followed by over-instrumentation to induce intracanal bleeding that presents a matrix and a source of growth factors necessary for tissue repair. In contact with this bleeding, the placement of a material such as MTA has in some cases induced pulp revascularization.

The multiplication of case reports published in the literature tends to demonstrate the clinical interest of pulpal revascularization

Table 1: Main growth factors of the dentine matrix and their potential for action.

Main growth factors of the dentin matrix	Function in revascularization
TGF-β1	Involved in primary odontoblastic differentiation and tertiary dentinogenesis
TGF-β2	Positively regulates the differentiation of DPSCs into mineral phenotypes
TGF-β3	Increases odontoblastic differentiation
BMP-2	Promotes odontoblastic differentiation *in vivo* and *in vitro*, and increases alkaline phosphatase activity
BMP-4	Increases odontoblastic differentiation
BMP-7	Promotes the differentiation of DPSCs into a mineral phenotype
Insulin Growth Factor (IGF)	Promotes the differentiation of DPSCs and SCAPs into a mineral phenotype
Platelet-Derived Growth Factor (PDGF)	Promotes angiogenesis and stem cell chemotaxis
Vascular Endothelial Growth Factor (VEGF)	Powerful angiogenic factor, promotes the formation of blood vessels
Epidermal Growth Factor (EGF)	Improves neuronal differentiation of DPSC and SCAP
Differentiation/growth factor 15	Promotes axonal regeneration and function after an attack and plays an important role in neural maintenance
Placenta growth factor	Promotes angiogenesis and osteogenic differentiation of stem cells
Adrenomedullin	Promotes the differentiation of odontoblasts by activating p38
Hepatocyte growth factor	Promotes the migration, proliferation and survival of stem cells
Neurotrophic Factor From The Brain (BDNF)	Promotes neuronal growth and axonal targeting
Neurotrophic factor derived from the Glial lineage	Promotes nerve regeneration *in vivo* and the survival/proliferation of pulp cells. Increasing the expression during odontogenic differentiation
FGF-2	Promotes stem cell angiogenesis and chemotaxis

therapies, but the variability of the results obtained leads to an interest in the nature of the biological tissue formed in the canal, and to ask the question whether the implementation of canal vascularization alone can be considered as a regeneration or a simple repair [22].

Some clinical cases report the return of tooth sensitivity, with positive responses to the vitality test, probably confirming the regeneration of nerve tissue within the tissue filling the canal, as well as a resumption of root growth and wall thickening [23-25].

All these elements therefore tend to suggest that real pulp tissue has been regenerated within the tooth. However, histological differentiation of the tissues formed remains impossible only with clinical and radiological examinations. The first objective is therefore to know the nature of the tissue formed, using hematoxylin eosin staining of samples taken after applying the pulp revascularization procedure to be able to identify the different types of cells constituting the newly formed tissue within the pulp canal. For this purpose, longitudinal cuts are made on the treated tooth, which will allow us to understand the fate of the pulp stem cells that were present in the root canal environment before the revascularization was applied.

A few weeks after a revascularization procedure, histological analysis shows that the root canal contains highly vascularized tissue similar to an apical papilla [26].

Several studies have observed three tissues within the revascularized endodontic: a cementoid tissue, a bone tissue and a periodontal ligament equivalent [27-29]. Others reported different results with either the absence of hard tissue in the canal or the presence of an odontoblastic layer in contact with the dentin [30]. This may be due to the persistence of living pulp tissue in the canal, which may be involved in the regeneration of the pulp [31]. Today, several hypotheses attempt to explain the phenomenon of endodontic revascularization:

1. Cells in the apical papilla survived pulpal necrosis by supplying blood to the apical papilla [26]. These cells proliferate and differentiate locally, causing root lengthening and thickening of the dentin wall (root maturation).
2. A part of the pulp cells of the root endodontic space has remained alive and, following revascularization, contributes to the maturation of the root.
3. In contact with the endodontic and dentine microenvironment, blood clot cells multiply and differentiate into fibroblasts, odontoblasts or cementoblasts [32].
4. Periodontal ligament cells proliferate in the periapex, migrate inside the root canal, then differentiate and deposit mineralized tissue on the inner dentin wall, from the lower third of the root to the apex. This is the most likely assumption today.

These observations suggest that the regenerated structure within the canal is closer to a periodontal tissue than to the original pulp tissue. This may be explained by the recruitment of cells from the periapical region that will differentiate in the revascularized endodontium into periodontal cells and not into pulpal fibroblasts or odontoblasts.

Physiological Changes Related to Pregnancy

During pregnancy, a woman changes. It prepares to receive a new being and bring him all the elements necessary for his development and growth. As soon as the implantation is completed, the hormonal profile of the pregnant woman is modified, which will allow the growth of the embryo and then the foetus. The key organ at the origin of this upheaval is the placenta.

Changes in a woman's body during pregnancy anticipate the future needs of the fetus, unlike the usual physiological responses of the non-pregnant body that occur in response to a need. This results in a transformation of the mother's homeostasis mechanisms with a modification of biological norms [33].

Pregnancy is characterized by a high serum concentration of growth factors (GH "growth Hormon", BMP "Bone Morphic protein", IGF-1 "insulin like growth factor 1", TGFβ "Transforming Growth Factor-β", etc.)

One week after fertilization, the blastocyst has exhausted its nutrient reserves, so its free life can only be of short duration [34]. It is then differentiated into an embryonic bud and a trophectoderm [35]. The latter then defines, with the maternal organism through an implantation process, a structure that will allow it to develop during pregnancy: the placenta. Thus, the placenta is a transitional organ essential for maintaining pregnancy and developing the fetes [36]. The human placenta is characterized by intense endocrine function; it has a high synthesis capacity but requires precursors from the fetes or mother and also has many hormone receptors. It thus develops steroid hormones, cytokines, glycoproteins, growth factors, and other proteins. Several peptides are produced, having a more or less known role in pregnancy.

Pregnancy is also characterized by other physiological changes.

The metabolism of the pregnant woman rises by 20% during the 3rd trimester of pregnancy. Pregnancy is characterized by a state of hyperinsulinism, due to hyperplasia and hypersecretion of islets of pancreatic cells and a state of peripheral insulin resistance caused by high levels of oestrogens and progesterone.

The liver shows increased synthesis of liver proteins, bile acids and steroidal precursors. Similarly, the oxidative pathway of cytochrome P450 is also stimulated. All this would be due to an increase in circulating oestrogen levels.

Significant variations in pituitary cells are also noted. The pituitary gland increases from 0.4 to 0.8 g or even to 0.12 g at the end of pregnancy. After lactation has stopped, the pituitary gland returns to about its size [37].

Serum prolactin levels rise gradually to be 5 to 10 times higher at the end of pregnancy. As its production increases, the production of Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH) (which are low during pregnancy) decreases. Oxytocin increases during pregnancy to 165 µg/ml. Its role in the physiological induction of labour is discussed, its secretion during labour is periodic and brief, and the frequency of peaks increases

as labour progresses. Oxytocin would have a regulating, but not an inducing role in induction of labour.

Adrenal glands show an increase in free cortisol levels.

In the thyroid, there is a slight swelling of the thyroid body, T3 and T4 levels are considerably increased, but their free and active fraction is not modified while the fraction related to globulin transport TGB is increased, due to an increase in the rate of the latter as well as an increase in its binding capacity. This shows that these hormones are transported to the fetes without any general effect of thyroid hyperactivity.

Very early in pregnancy there is an increase in cardiac labour. Cardiac output increases by about 30 to 50%. It depends on 2 factors: the heart rate which increases by 15% (15 to 20 bpm over time), and the systolic ejection volume which increases by 30% (+10 to 15 ml). Venous pressure in the upper limbs does not vary but increases considerably in the lower limbs, while central venous pressure is not modified.

During pregnancy; there is an increase in pulmonary blood flow and an increase in oxygen uptake per minute. The pregnant woman's oxygen requirements increase by 15% with a slightly modified respiratory rate but a 40% increase in tidal volume depending on the expiratory reserve volume. The removal of CO_2 is therefore high, and therefore the pressure of arterial CO_2 is reduced. Progesterone is responsible for this "dyspnea" by acting on the respiratory centres.

The plasma volume gradually increases throughout pregnancy as well as the total mass of red blood cells, which promotes a massive conduction of hormones and growth factors secreted during pregnancy. The increase in erythrocyte mass covers the additional O_2 requirements to all organs of the body.

Like the rest of the body, the oral state is affected by these changes caused by pregnancy.

Hormonal impregnation during pregnancy (increased progesterone and oestrogen levels) causes an increase in the prevalence of gingivitis.

Dietary changes; nausea and vomiting in the 1st trimester, then gastroesophageal reflux of the last trimester lead to meal fragmentation next to high acidity.

Discussion and Conclusion

Under certain pathological conditions, pulpal vascularization is interrupted, resulting in necrosis.

To revascularize the tooth, this pulpal revascularization process relies on several essential points, including the presence of stem cells, and biological mediators (hormones and growth factors) to direct the differentiation of pulpal stem cells towards a well-defined cell line.

The success of this new therapeutic approach depends on several other physico-chemical parameters, such as pH, the oxygen content present in the pulp environment, the nutrients required for the proliferation of pulp stem cells, as well as the concentration of the biological messengers involved.

Based on a physiological observation, some hormonal changes have been observed during pregnancy that will promote the pulp revascularization mechanism, because the mediators of cell and tissue differentiation and proliferation are secreted at a higher level in pregnant women, thus ensuring the development of fetal tissues and cells, but also the repair and regeneration of damaged, or even lost tissues of the carrier mother.

Physiological changes during pregnancy will also contribute to this mechanism.

Like other cells in the body, pulp stem cells require oxygen to be available to ensure its biological functions, including division and differentiation, which will be promoted during pregnancy since during this rather special period the oxygen content increases remarkably, linked to the increase in blood flow which allows the massive conduction of oxygen by erythrocytes, but also the growth factors and nutrients necessary for the success of pulp revascularization therapy.

Indeed, pregnancy presents a quite special period for healing and regeneration therapies, it is characterized by a high serum concentration of growth factors and a remarkable increase in stem cell stock, are the consequence of the adaptation of the carrier mother's body necessary for good embryogenesis, pregnancy is then the only period that promotes the regeneration mechanisms in an adult person.

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